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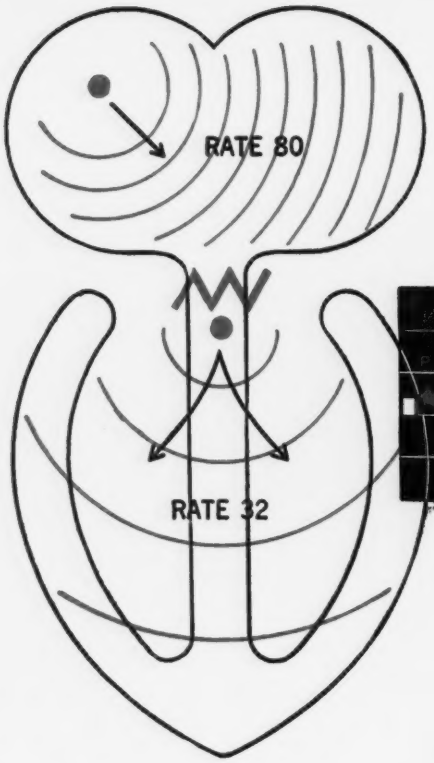

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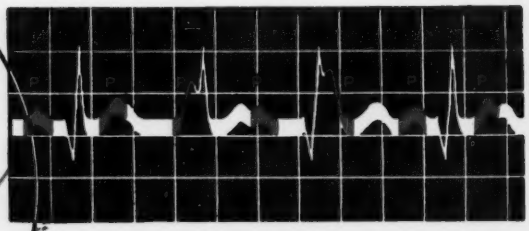

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1. Nathanson, M. H., and Miller, Harold: *California Med.*, 76:370, June, 1952.
2. Nathanson, M. H., and Miller, Harold: *Circulation.* 6:238, Aug., 1952.

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Reactivation of Rheumatic Fever Following Mitral Commissurotomy

By Louis A. Soloff, M.D., Jacob Zatuchni, M.D., O. Henry Janton, M.D., Thomas J. E. O'Neill, M.D., and Robert P. Glover, M.D.

A febrile syndrome following mitral commissurotomy is described. This syndrome consists of the episodic recurrence of a combination of events first occurring after a variable latent phase following mitral commissurotomy and is uniformly characterized by precordial pain and fever, is commonly featured by the precipitation or intensification of pre-existing heart failure, is variably accompanied by migratory joint pains, arrhythmias, hemoptysis or psychosis and sometimes terminates in death. The syndrome was found to occur in 43 (24.0 per cent) of 179 consecutive individuals subjected to mitral commissurotomy. Because we have never encountered such a syndrome following any other type of nonrheumatic cardiac or pulmonary surgery and for other reasons we are compelled to regard it as a reactivation of rheumatic fever.

MITRAL COMMISSUROTOMY is a procedure that was designed to relieve obstruction at a mitral valve damaged by rheumatic fever.[1] It is not intended to control the rheumatic state. On the contrary, a surgeon performing a mitral commissurotomy operates in a field that is potentially the seat of subclinical active infection. So long as there is no specific method of controlling rheumatic fever the possibility exists that such an operation may activate rheumatic infection to clinical recognition or spread rheumatic fever subclinically. This implicit fear forms the basis for the almost universal acceptance of clinically active rheumatic fever as a contraindication to mitral commissurotomy.

Yet, it is well known that progressive rheumatic cardiac deterioration may occur in individuals in whom rheumatic activity cannot otherwise be recognized on clinical grounds and who, at necropsy, have characteristic stigmata of active rheumatic carditis. Indeed, it is because of the frequency of such findings at necropsy in children or adolescents dead of cardiac failure due to rheumatic heart disease, that many students of rheumatic fever think that any rheumatic child or adolescent with progressive cardiac failure has active rheumatic carditis.[2] One could anticipate, therefore, an occasional postoperative unmasking of obviously clinically active rheumatic fever in individuals who were preoperatively regarded as having inactive or doubtfully active rheumatic fever. We have seen such occurrences. Fortunately, in our experience, they are rare, perhaps because of the care used to exclude from operation individuals who have any manifestations that can be interpreted as possibly due to active rheumatic fever.

However, we have observed a distressingly high incidence of a combination of events that occurs after a variable latent period following mitral commissurotomy. As far as we know, this combination of events, which has as its common denominator pain and fever, does not occur following any other type of nonrheumatic cardiac or pulmonary surgery. The purpose of this report is to describe the incidence and

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character of these events that we are compelled to regard as a reactivation of rheumatic fever.

Material

The records were examined of 183 consecutive individuals subjected to mitral commissurotomy. Four were excluded because of the immediate precipitation by operation of active rheumatic fever. None of the other 179 was regarded preoperatively as having active rheumatic fever even in retrospect. Of these 179, 67 (37.4 per cent) had pain of delayed onset after discharge from the hospital. Of these 67, 43 (24.0 per cent of the 179) were recognized to have pain and fever of delayed onset. The character of the delayed pain occurring in those with pain alone was similar to that occurring in those with pain and fever. Although we have some evidence to suggest that in those with pain of delayed onset without recognized fever, the presence of fever may have been overlooked or suppressed by medication, only those 43 individuals with pain and fever of delayed onset form the basis of this report. The follow-up period varies from 6 to 24 months.

Characteristics of the Pain and of the Fever of Delayed Onset

Pain. Pain of delayed onset is most easily recognized when it occurs in an individual whose incisural pain has subsided considerably in intensity. After the gradual subsidence of incisural pain over a period of 10 days to 4 weeks, the individual is often terrified by the abrupt onset of severe pain. When pain appears to be an intensification of incisural pain or insidiously replaces the incisural pain, its true nature may not be recognized until one is struck by its changing character or location or until fever is found to be present.

The pain is variously described as dull, aching or more commonly bone-crushing, excruciating, knife-like, vise-like, as severe tightness or as a sensation as if "an elephant stepped on one's chest." Pain is commonly localized to the precordial area, particularly to the lower left parasternal region. It may radiate to the back, particularly to the left infrascapular region, to the epigastrium, to the left shoulder, to the left side of the neck or even to the left side of the upper jaw. It may start in the upper jaw and mimic a tooth abscess, its true nature being recognized only later when radiation occurs and localization to the precordial area takes place. It may radiate to both shoulders or across the entire anterior chest wall. Pain is usually aggravated by change of body position, by deep breathing and by swallowing. Pain is modified but not completely relieved by ordinary analgesics. Pain with variation in intensity may last from 10 days to 4 weeks. After an interval of freedom from pain for two weeks to one month, pain may recur and follow more or less closely the temporal course of the bouts of fever that will be described next.

Fever. Fever, if recognized, usually appears synchronously with pain. At times, fever may precede or follow by a day or two the appearance of pain. Fever usually rises slowly to 100 to 102 F. Rarely, it rises abruptly to as high as 104 F. The temperature varies daily from 1 to 3 degrees. It may remain elevated for 10 days to 4 weeks. Most patients are extremely enervated and toxic. Some perspire so profusely that pajamas and bed linen have to be changed several times a day. In others, perspiration is not noteworthy. Fever can be lowered and occasionally brought to normal by salicylates. Adrenocorticotropic hormone tends to be antipyretic. In no instance was an unrelated illness uncovered to account for the fever.

The patient may have one such bout or, more commonly, after an interval of one to four weeks of freedom from fever, another similar cycle may be ushered in. About an equal number of patients have had two, three and four bouts, several have had five and seven bouts and one had 14 bouts.

The syndrome of pain and fever of delayed onset following mitral commissurotomy has been divided into eight groups according to the associated clinical findings.

1. Bouts of Pain and Fever Uncomplicated by Other Clinical Phenomena

This group consisted of six individuals. Aschoff bodies were found in two of the six biopsies of the left auricular appendage. Of the others, three showed hypertrophy and the remaining one a degenerative reaction. Fever and pain were the only clinical manifestations. There was no precipitation or exacerbation of heart failure. There were nonspecific labora-

tory signs of infection. The electrocardiogram showed T-wave changes. No additional cardiac medication was required. Two received adrenocorticotropic hormone and one of these two also received cortisone during another bout with subsequent improvement but not with complete relief of pain or fever.

The following case, characteristic of this group, also illustrates the recurrent episodic nature of this syndrome.

Case 1. M. E., a 41 year old white female, was first admitted to the Episcopal Hospital on Oct. 10, 1952 for mitral commissurotomy. She had known of a heart murmur since the age of 5 when she had had St. Vitus' dance. She suffered a left cerebrovascular embolus on Aug. 19, 1951. Following this event, shortness of breath developed slowly and progressively.

Physical and roentgenologic studies were typical for mitral stenosis. The electrocardiogram disclosed auricular flutter with a ventricular rate of 100 per minute. Venous pressure was 180 mm. (fluid). The ether time was six seconds and the Decholin time 55 seconds. Blood count and urinalysis were normal. The sedimentation rate was 10 mm. in one hour (Wintrobe).

The ventricular rate was slowed by digitalis and the auricular flutter changed to flutter-fibrillation.

A mitral commissurotomy was performed on Oct. 30, 1952. Biopsy of the left auricular appendage disclosed only a degenerative reaction. Postoperatively, the patient responded satisfactorily. She was discharged on Nov. 14, 1952, to continue convalescence at home.

Two weeks later, she began to experience chest pain. It was sharp and localized to the left precordial area and aggravated by swallowing, breathing or movement. There was usually constant aching, frequently with superimposed recurrent attacks of sharp pain, "like a vise pushing in front and back." Sweating was frequent and profuse. Because of increasing pain and lack of relief by salicylates, she was readmitted to the hospital on Dec. 3, 1952. She was in marked distress. Respirations were increased in rate but voluntarily reduced in depth because of pain. She was pallid but not cyanotic. The veins were not distended. The precordial area was tender. The cardiac impulse was palpable in the fifth intercostal space 2 cm. to the left of the midclavicular line. The rhythm of the heart was grossly irregular at an average ventricular rate of 100 per minute with a pulse deficit of 10 per minute. There was no friction rub. A diastolic rumbling murmur was audible at the apex. The second sound at the pulmonic area and the first sound at the apex were accentuated. There was no friction rub. The liver and spleen were not palpable. There was no edema. The blood pressure was 110/80. The oral temperature was 100 F.

Chest roentgenogram disclosed considerable cardiac enlargement. A few linear strands were seen in the right lower lobe. An electrocardiogram showed auricular fibrillation and ST-T changes. The S-T segment was depressed and the T wave was inverted in the left chest leads. The leukocyte count was 12,500 per cubic millimeter with 80 per cent neutrophils. The sedimentation rate was 42 mm. in one hour. Urinalysis was negative. Antistreptolysin titer was 1:48 and antihyaluronidase titer was less than 1:24. The venous pressure was 165 mm. (fluid). The ether time was 17 seconds and the Decholin time 22 seconds.

Treatment was symptomatic. Temperature returned to normal in four days. Pain gradually subsided over a period of 10 days. Repeated electrocardiograms were similar except for a change of the ventricular rate to slower levels. She was discharged on Dec. 19, 1952. Digitalis dosage was maintained.

Again she remained at bed rest at home. She felt tired. In one week precordial pain, similar in character to that experienced previously, reappeared. Sweating was profuse. She was readmitted to the hospital on Jan. 3, 1953. Examination revealed pallor but no dyspnea. The heart was enlarged to the left. Presystolic and systolic murmurs were audible at the apex. Fever was present. Chest roentgenogram disclosed no further increase in heart size. An electrocardiogram showed increased negativity of the T waves in the left chest leads. The venous pressure was 130 mm. (fluid). The ether time was 15 seconds and the Decholin time 17 seconds. The leukocyte count was 9300 per cubic millimeter with 73 per cent neutrophils. The sedimentation rate was 38 mm. in one hour. Blood cultures were sterile. Antistreptolysin titer was 1:32 and antihyaluronidase titer was less than 1:24. Temperature remained elevated, reaching 104 F. rectally. Pain was severe. Penicillin and salicylates were ineffectual. Adrenocorticotropic hormone (5 mg. in 1000 cc. of 5 per cent glucose in water) was administered intravenously on Jan. 9, 1952, and resulted in moderate relief of pain. Thereafter, symptoms gradually subsided and she was discharged on Jan. 14, 1953.

One week later, pain reappeared. At first, it was aching in character. Temperature was occasionally elevated to 100 F. In the following week, pain increased in severity. The patient was readmitted to the hospital on Jan. 29, 1953. Examination revealed the cardiac impulse to be in the fifth intercostal space slightly to the left of the midclavicular line. The rhythm was grossly irregular at an average ventricular rate of 100 per minute with a pulse deficit of 5 per minute. A diastolic rumble with accentuation of the first sound and a slight systolic murmur were heard at the apex. The lungs were clear. There was no evidence of failure. Chest

roentgenogram revealed no significant changes. An electrocardiogram was similar to the one taken previously. The leukocyte count was 7750 per cubic millimeter with 75 per cent neutrophils. There was a mild anemia. The sedimentation rate was 40 mm. in one hour. Blood cultures were sterile. No "L. E." cells were found. Antistreptolysin titer was 1:32 and antihyaluronidase titer 1:24. Temperature remained elevated for three days. Salicylates were without effect upon the pain. Cortisone was administered for a few days with moderate amelioration of the pain. Repeated chest roentgenograms and electrocardiograms were similar to those taken previously. Chest pain gradually subsided during hospitalization. The sedimentation rate gradually decreased and on February 17 was 5 mm. in one hour. Body weight remained essentially unchanged. She was discharged on Feb. 19, 1953, to continue convalescence at home.

Since discharge, she has remained afebrile and has gradually increased her activities. For a few weeks, she continued to experience a dull aching sensation in the precordial region and occasionally required salicylates for relief. At present, she has no pain or fever and states that she has not felt as well in years.

A graphic presentation of the temperature record and of other pertinent findings is shown in figure 1.

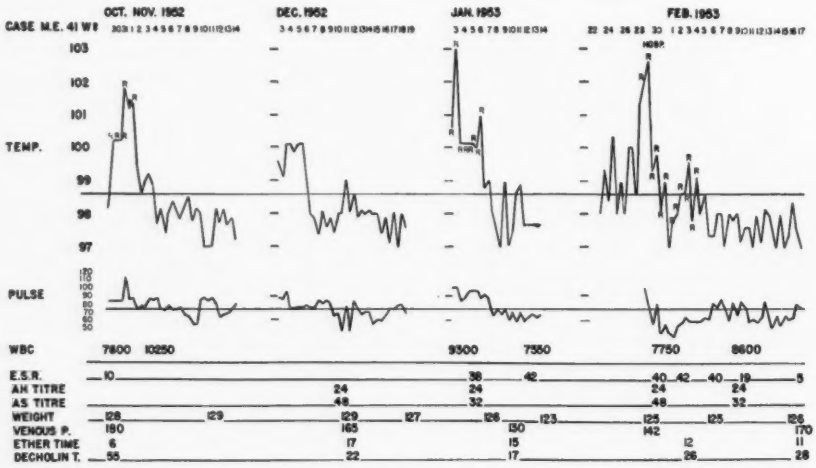

FIG. 1. *Case 1.* (*M. E.*) Chart of temperature, pulse, body weight and laboratory data during repeated hospitalizations because of the postcommissurotomy febrile syndrome. Mitral commissurotomy was done on Oct. 30, 1952. The temperature was elevated three to seven days prior to each hospitalization. E.S.R. refers to the erythrocyte sedimentation rate, AH to the antihyaluronidase titer and AS to the antistreptolysin titer.

2. Bouts of Pain, Fever and Psychoses

This group consisted of four individuals. Aschoff bodies were found in one of the two biopsies of the left auricular appendage. Three requiring digitalis preoperatively required an identical amount after operation. Neurologic findings suggestive of a focal cerebral lesion were not present. We cannot elaborate on the nature or significance of the psychoses. We do not know whether it was a depressive reaction to the operation, a manifestation of rheumatic brain disease,[3] unrecognized cerebral emboli, or whether, as suggested by one of the cases, the psychosis was an accentuation of one not recognized preoperatively.

3. Bouts of Pain, Fever and Heart Failure

This group consisted of eleven individuals. Aschoff bodies were found in two of nine biopsies of the left auricular appendage. The others showed hypertrophy and, in addition, in one a thrombus. During the bouts, these individuals not only had pain and fever but heart failure as well. In all instances, heart failure was of the combined right and left type. Left heart failure was partly masked by pain. The objective signs were almost invariably predominantly those of right heart failure. Indeed, these findings were so striking in some instances that the possibility of cardiac

tamponade due to rheumatic pericarditis with effusion was considered, at least, as a contributory factor. However, the cardiac size, although larger than that present preoperatively, was not increased to the extent that one could seriously entertain, on the basis of roentgen findings, the presence of sufficient fluid in the pericardial sac to embarrass the circulation. In some individuals, residual distension of the neck veins and hepatomegaly persisted. In such individuals, we are strongly suspicious of the surgical production of an increase in mitral regurgitation. We believe so because in three instances, not included in this series, in which an immediate significant mitral regurgitation was produced, not only was dyspnea increased, but a large liver and bulging neck veins appeared. In these individuals, dyspnea was partly controlled by medication but the signs of right heart failure were constant.

The following recent case not included in our tables illustrates the type of heart failure seen in this group.

Case 2. A. F., a 46 year old white woman, was first seen by one of us (L.A.S.) on June 11, 1946, because of pain in the substernal and left infrascapular regions, palpitation and dyspnea while climbing steps.

Physical and roentgenologic studies (fig. 2) were typical of a mitral stenosis. The electrocardiogram disclosed many premature auricular beats and deformed P waves. On March 25, 1947, she developed permanent auricular fibrillation. Over the succeeding years her symptoms waxed and waned until Sept. 1, 1952 when she developed progressive dyspnea that terminated in an attack of pulmonary edema during the first week in October.

Mitral commissurotomy was performed on Oct. 23, 1952. The patient had an uneventful postoperative course except for the usual incisural pain and left the hospital in 10 days.

Two weeks after discharge, she was seized with severe pain in the left lower parasternal region which radiated up into the left side of the neck. Pain also shot across the entire anterior chest wall to the right shoulder.

Physical examination revealed that she had gained 10 pounds since discharge from the hospital. The neck veins bulged. The cardiac impulse was in the fifth intercostal space slightly to the left of the midclavicular line. The rhythm was grossly irregular at a ventricular rate of 100 per minute with a slight pulse deficit. A precordial systolic murmur was present and loudest (grade 2) at the apex where a presystolic murmur was also heard. The first sound at the apex and the second sound at the pulmonic area

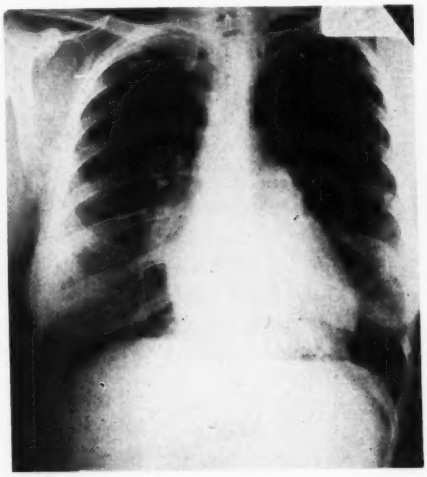

FIG. 2. *Case 2.* (*A. F.*) Preoperative chest roentgenogram, P-A view. There is slight cardiac enlargement, prominence of the pulmonic segment, increased hilar markings, left auricular enlargement and calcification in the region of the mitral valve.

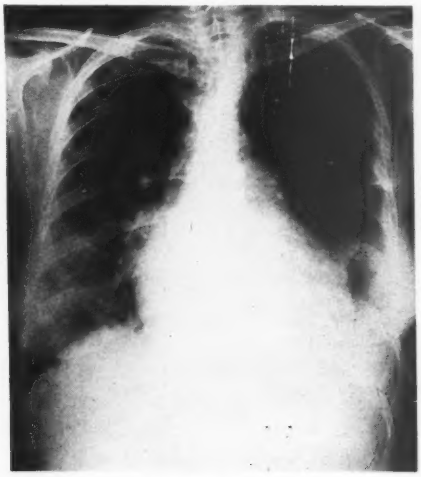

FIG. 3. *Case 2.* (*A. F.*) Chest roentgenogram, P-A view, two months postoperatively. There is an overall increase in the size of the cardiac silhouette.

were accentuated. Subcrepitant rales were present at the lung bases. The liver was enlarged and tender and when pressed resulted in increased distension of the neck veins. The legs appeared full, the skin being tight and shiny, but pitting edema could not be demonstrated. Her temperature was 101 F. The antihyaluronidase titer was 1:96 and antistreptolysin titer was 1:48.

She was placed upon a strict salt-poor diet, acetylsalicylic acid and codeine. Acetylsalicylic acid lowered the temperature by 1 to 2 degrees. Fever persisted for 10 days. Several times the patient thought her temperature was normal and stopped taking acetylsalicylic acid only to find it rise in the next few hours to above normal. After a two-week interval of freedom of fever, fever recurred and was present off and on until the first week of January, 1953.

Roentgenographic study on Dec. 21, 1952, showed an overall increase in size of the cardiac silhouette and possibly even of the left auricle (fig. 3).

The patient, in addition to digitalis and a salt-poor diet, requires mercurial injections about once in 10 days. The neck veins are still abnormally distended and the liver is palpable. She had less dyspnea and was otherwise comfortable except for tightness across the upper half of her abdomen and increasing dyspnea about every eight or nine days after a mercurial injection. On May 27, 1953, at 2 a.m. she developed an attack of pulmonary edema that, she states, was similar in every way to the attack she developed before operation.

4. Bouts of Pain, Fever, Heart Failure and Arrhythmia

This group of 12 individuals had the highest incidence of biopsies positive for the presence of Aschoff bodies, 7 of 11 left auricular appendages examined. Of the other four, one showed hypertrophy, two were reported as normal and one was the seat of hemorrhage. The arrhythmias noted were rapid ventricular rate uncontrollable with digitalis in one, multiple ventricular ectopic beats in another, recurrent paroxysmal auricular tachycardia in two, auricular fibrillation in seven and auricular flutter followed by auricular fibrillation in one. This last patient required massive doses of digitalis to control the ventricular rate. Quinidine sulfate converted auricular fibrillation in one individual back to sinus rhythm. All arrhythmias were associated with a precipitation or intensification of heart failure. The one who did not require digitalis before operation required it during the bouts and still does. All required additional cardiac medication.

It is noteworthy that 10 of these 12 individuals had a sinus rhythm before operation. A change in rhythm from a sinus mechanism to auricular fibrillation is frequently easily recognized by both the physician and the patient. On the other hand, changes from auricular fibrillation to a different arrhythmia or additional arrhythmias such as multiple ectopic beats are difficult to recognize without electrocardiographic evidence or unless the rate becomes exceptionally fast. It is possible, therefore, that changes in rhythm in this syndrome are commoner than we report.

The case reported in group 6 also illustrates this type.

5. Bouts of Pain, Fever, Heart Failure and Arthritis

This group included three individuals. Biopsy of the left auricular appendage revealed Aschoff bodies in one, enlarged blood vessels in another, and dense collagenous material in the third. The arthritis was typically migratory. The joints were painful and tender but not red, hot or markedly swollen. In these individuals, the heart rhythm was not changed during the febrile bouts. The rheumatic nature of this affection may be recognized by the patient because of its similarity to a previous naturally occurring attack of rheumatic fever with joint manifestations. One of these three experienced bouts monthly for 14 months.

The following case illustrates the features of this group.

Case 3. F. K., a white female, 42 years old, was first seen by one of us (L.A.S.) on Jan. 25, 1945. She had rheumatic fever at the age of 11 years. In 1938, she was digitalized because of severe dyspnea. In the ensuing years, her symptoms waxed and waned but increased for the last three months before operation, so that mercurial injections were used once and, at times, twice a week. Clinical and roentgenologic studies were typical for mitral stenosis. Electrocardiogram revealed auricular fibrillation. Other laboratory studies were normal.

On April 17, 1952 a mitral commissurotomy was done. Biopsy of the left auricular appendage showed dense collagenous material but no Aschoff bodies. The postoperative course was uneventful. An elec-

trocardiogram showed increased depression of the S-T segment and inverted T waves in the left chest leads. She was discharged on April 30, 1952.

On May 8, 1952, pain in the chest appeared. Pain was substernal in location and occasionally severe but usually more of a sensation of tightness. Occasionally, she experienced mild aching of the joints. Fever was present and varied from 99 to 102 F. On July 9, 1952, the temperature was 102 F. and severe migratory joint pains affecting the shoulders, elbows, hips and knees were present. She volunteered that "it felt like my childhood rheumatic fever." She was extremely tired and had an almost constant sensation of near collapse. The leukocyte count was 8800 per cubic millimeter and the hemoglobin 11 Gm. per 100 cc. She was seen frequently in the following months. Joint pains accompanied by fever were almost constantly present. The neck veins were distended and hepatomegaly and edema were present. During the first week in October, all joint pain disappeared and the temperature returned to normal.

She is on a maintenance dose of digitalis and is almost entirely free of symptoms. She volunteered the information that she was able to walk even in cold weather against a mild wind without dyspnea for the first time in years. She has required no mercurial injection since recovery from the febrile syndrome.

6. *Bouts of Pain, Fever, Heart Failure, Arrythmia and Arthritis*

This group consisted of two individuals. Biopsy of the left auricular appendage showed Aschoff bodies in one and endocardial thickening and a slight increase in cellularity in the other. Both individuals were on maintenance doses of digitalis and had a sinus rhythm preoperatively and postoperatively. During the febrile bouts, irregular heart action and overt heart failure occurred. An electrocardiographic study was done in one of these and revealed auricular fibrillation. The arrhythmias in these two individuals were transient. Sinus rhythm reappeared spontaneously after subsidence of the febrile episode. The joint pains were severe and protracted.

The following case shows the features of this group.

Case 4. S. N., a 36 year old white female, was first seen by one of us (L.A.S.) on March 8, 1951. She had been told eight years previously that she had rheumatic heart disease but was free of symptoms until July 1950 when she developed dyspnea on effort. Clinical and roentgenologic studies (fig. 4) were typical of mitral stenosis. During March and April, 1952 dyspnea became progressively worse.

She elected surgery, and mitral commissurotomy was done on May 15, 1952. Biopsy of the left auricular appendage failed to reveal Aschoff bodies. Postoperatively, a friction rub was heard in the left parasternal region. Otherwise, the postoperative course was uneventful. Chest roentgenogram on May 27 showed a slight increase in the over-all size of the heart, haziness of the left base and a strand-like density in the right lung field. Electrocardiogram

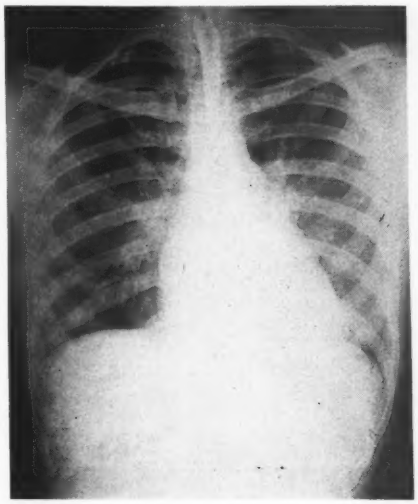

FIG. 4. *Case 4.* (*S. N.*) Chest roentgenogram, P-A view, May 9, 1952, preoperatively. There is slight cardiac enlargement. The aortic knob is small. The pulmonary artery segment is enlarged and convex. The left auricle is enlarged. The hilar areas are prominent. The left lower hemithorax is hazy.

on May 26 (fig. 5) showed a prolonged P-R interval of 0.27 second. In leads III and aV_F, J was slightly elevated, the S-T segment was convex upward and the T wave was sharply inverted. She was discharged on May 27, 1952, to continue her convalescence at home.

Two days later she developed pain in the left side of the neck and face, centering in the left upper gum. The next day, she developed a fever of 102 F.

Because of persistence of pain and fever, she was readmitted to the Episcopal Hospital on June 2, 1952. Examination of the mouth, teeth and face was negative. There were rales at both bases of the lungs. The heart was slightly enlarged. The second pulmonic sound was accentuated. An apical systolic murmur was present. On admission, the leukocyte

count was 20,000 per cubic millimeter with 75 per cent neutrophils. Urinalysis was negative. Temperature varied from 99 to 101 F. for nine days. She perspired frequently. Pain, which at first was located in the left side of the face, now appeared to be radiating to this region from the retrosternal area and was described as a severe pressure sensation. Chest

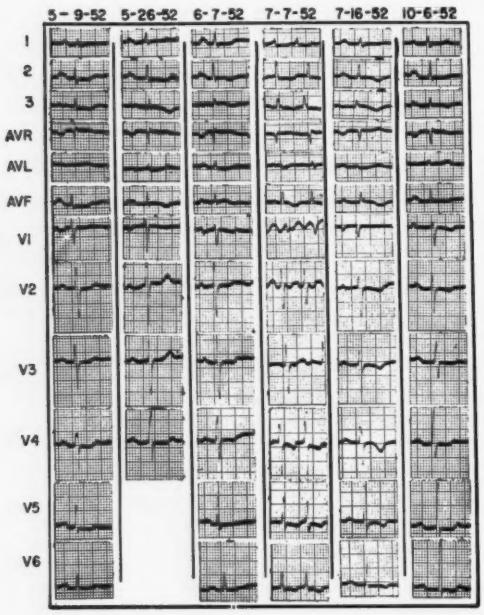

FIG. 5. *Case 4.* (*S. N.*) Electrocardiograms taken on the various dates shown at the top of the tracings. Mitral commissurotomy was done on May 15, 1952. All of the tracings show sinus rhythm with the exception of the one taken on July 7, 1952, which shows auricular fibrillation. The P-R interval is prolonged in all of the tracings except those taken on May 9, 1952 and June 7, 1952. The tracings on June 7, 1952, July 7, 1952 and July 16, 1952 were taken during hospitalization for the postcommissurotomy febrile syndrome. Note the ST-T alterations consistent with a pericarditis and a myocarditis. Digitalis dosage was constant throughout except during the bout of auricular fibrillation when it was temporarily increased. Quinidine was given only on July 14, 1952 and July 15, 1952.

roentgenogram on June 5 revealed no significant changes. An electrocardiogram on June 7, (fig. 5), showed slight rotation of the P axis to the left with increased voltage of the P wave. The P-R interval was 0.20 second. The QRS axis was also shifted slightly to the left. The S-T segment was definitely elevated and convex upwards in leads III and aV_F. T waves were decreased in voltage. Chloromycetin, analgesics and acetophenetidin were administered and digitalis dosage maintained. Pain gradually subsided and temperature returned to normal on June 12. Chest roentgenograms on June 14 revealed no significant change. She was discharged on June 17, 1952.

She returned to the office on July 3, 1952, complaining of pain in all the joints with stiffness of the adjacent areas, fatigue, profuse perspirations and a sensation of recurrent "jumping" heart beats. Temperature was 100 F. The heart rate was regular at 100 per minute. A friction rub was audible in the apical area. She was advised to rest in bed and to take acetylsalicylic acid and codeine sulfate.

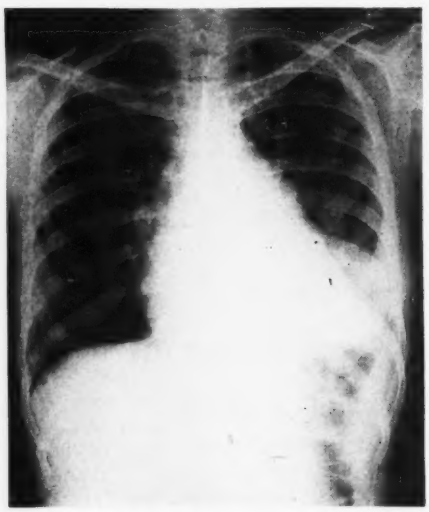

FIG. 6. *Case 4.* (*S. N.*) Chest roentgenogram, P-A view, July 7, 1952. The cardiac silhouette is much larger than previously.

Because fever, pain and sweating increased, she was readmitted on July 7, 1952. An electrocardiogram on the day of admission, (fig. 5), showed the presence of auricular fibrillation at an average ventricular rate of 150 per minute with occasional ectopic ventricular beats. The leukocyte count was 8300 per cubic millimeter with 73 per cent neutrophils. Hemoglobin was 11.8 Gm. per 100 cc.; erythrocytes numbered 3.81 million per cubic millimeter, and hematocrit was 40 per cent. Blood culture was sterile. A chest roentgenogram on July 7, (fig. 6), showed an increase in size of the cardiac silhouette. Penicillin and salicylates were administered. Additional digitalis was necessary for control of the ventricular rate. Quinidine sulfate was given daily (0.2 Gm. every three hours for five doses) on July 14 and July 15. An electrocardiogram on July 16 (fig. 5) showed a sinus rhythm. The P-R interval was prolonged to 0.27 second. Temperature

was 98 to 101 F. for two days and then was usually normal. She was discharged on her usual maintenance dose of digitalis on July 16, 1952.

On August 7, 1952, she returned to the office complaining of pain in the ankles and knees. Milder pain was present in the wrists upon motion. There was fatigue on effort and shortness of breath on lifting light objects. Temperature was 99.2 F. Recurrent mild joint pains and severe chest pain with fever persisted until September 10. At this time, she was afebrile and completely free of joint pains and able to walk five city blocks without discomfort. An electrocardiogram on October 6 (fig. 5) showed a sinus rhythm. The P-R interval was 0.24 second. The S-T segment was now isoelectric in leads III and aV_F. The T waves were now positive in the left chest leads.

On Sept. 10, 1952, she became free of symptoms. She improved functionally and was able to dance on two different occasions. On October 16, digitalis was discontinued. She remained well until December 12, when joint pains and fever recurred. She became more tired and dyspneic. Fever and joint pains disappeared on Feb. 3, 1953, but dyspnea and fatigue continued to be present. She was redigitalized but states that she feels no better than she did before operation.

7. Bouts of Pain, Fever, Heart Failure and Hemoptysis

This group included two individuals. Biopsy of the left auricular appendage in one showed hypertrophy. One had three episodes of hemoptysis and the other had only one. Other than the hemoptysis, the findings were similar to those observed in group 3.

8. Bouts of Pain, Fever and Heart Failure Terminating in Death

This group included three individuals. Biopsy of the left auricular appendage in all three revealed only hypertrophy. Each individual had a delayed onset of pain and fever with progressive and intractable heart failure terminating in death. Necropsy was performed in one of these and revealed active rheumatic carditis.

A summary of these reactions and their incidence is shown in table 1.

Laboratory Findings

Neither we, nor the referring physicians, were successful in our search for causes of this reaction other than the operative procedure. None gave a history of a preceding sore throat, upper respiratory infection or any unrelated infection. Laboratory data on five individuals who consented to repeated hospitalization during the reactions failed to produce illuminating data. The leukocyte count varied from normal to 20,000 per cubic millimeter, with an average of 11,000 per cubic millimeter. The erythrocyte sedimentation rate (Wintrobe) was moderately increased to an average of 23 mm. in one hour. Cultures of the blood, throat, sputum and urine were all negative.

Table 1.—*Postcommissurotomy Febrile Syndrome of Delayed Onset—Incidence, 24.0%*; Summary of 43 Cases*

Fever Only	6
Fever and Psychosis	4
Fever and Heart Failure	11
Fever, Arrhythmia and Heart Failure	12
Fever, Arthritis and Heart Failure	3
Fever, Arthritis, Arrhythmia and Heart Failure	2
Fever, Hemoptysis and Heart Failure	2
Fever, Heart Failure and Death	3

* 67 of 179 persons subjected to mitral commissurotomy had recurrent chest pain after discharge from the hospital. In 43 of these, the febrile syndrome occurred.

In all instances where roentgenologic studies were available, the cardiac silhouette appeared to be slightly larger during the syndrome and subsequent to it than it was before operation. The silhouette was increased in all its diameters except, at times, along the left border in the region where presumably the left auricular appendage was before amputation. During the febrile stage, the individual chambers may not be so clearly demarcated from one another as they were previously or subsequent to the reaction.

The electrocardiographic changes noted during the febrile syndrome were (1) occasional prolongation of the auriculoventricular conduction time, (2) S-T segment changes which are suggestive of pericarditis or appear to be by comparison with previous tracings, (3) S-T segment changes suggestive of increased myocardial derangement, (4) lowering of the voltage of T or greater negativity of T and prolongation of Q-Tc, suggestive also of

increased myocardial derangement, (5) transient or permanent auricular fibrillation, (6) increased ventricular rate, and (7) auricular or ventricular ectopic beats or both.

Discussion

Unfortunately, there is no specific test for rheumatic activity. We realize full well the difficult differential diagnosis of rheumatic fever, greatly enhanced by the effects of an operation upon the heart. The diagnostic problems arising in the immediate postoperative period are particularly difficult and will be the subject of a subsequent report. It is, however, inconceivable to us that the delayed phenomena we have described are simply manifestations of surgical trauma. Rather, we look upon the surgical operation as a trigger mechanism that sets in motion a series of events that in time rise to clinical manifestations. The pathogenesis of this mechanism at this time is purely speculative. We can think of several possibilities:

1. Operation in some manner permits the spread of endogenous streptococci that, after a variable latent period, causes the appearance of the delayed syndrome. This hypothesis was suggested to us by Dr. T. N. Harris.

2. Operation makes the individual more susceptible to mild and subclinical streptococcal infections.

Hypotheses 1 and 2 are now being tested by Dr. Harris by immunologic studies of individuals before and following mitral commissurotomy.

3. Surgical incision of inflammatory tissue directly spreads inflammatory agents that multiply and, after a latent period, give rise to clinical symptoms.

4. Surgical incision permits the escape of abnormal protein material to which the body responds after a variable time by the production of immune bodies with clinical manifestations.

Both 3 and 4 appear unlikely to us because the reaction is not a single one but frequently is of a cyclic or repetitive type.

5. This syndrome is another example of the hypersusceptibility of the rheumatic individual to nonspecific stimuli.

Almost from the beginning of the recognition of rheumatic fever, there have been sporadic reports of the relationship of trauma to not only rheumatic activity but its initial site. Drewitt,[4] Bland and Jones,[5] Swift,[6] and Massell, Mote and Jones[7] have commented upon this relationship. The last observers have produced in subjects with rheumatic fever subcutaneous nodules, clinically indistinguishable and histopathologically similar to spontaneous ones, by the injection of autologous blood into the subcutaneous and deep tissues in the region of the olecranon process followed by the application of frictional pressure.[7, 8] The more active the rheumatic fever, the larger the induced nodule and the longer its duration.

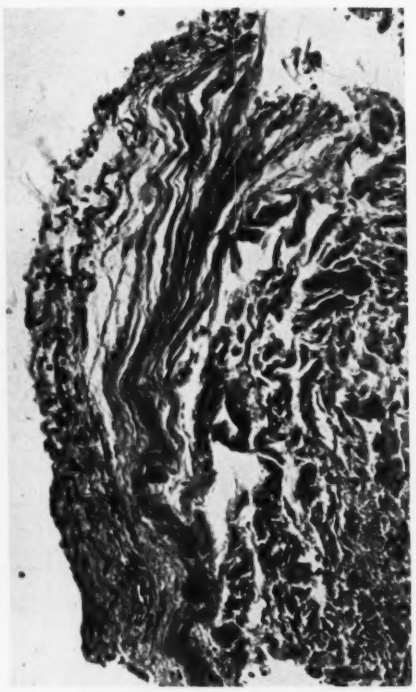

Fig. 7. Section of mitral valve at site of commissurotomy (200 ×). Note the red blood cells which appear as black dots on the left.

We have seen masses of red blood cells in the mitral valve beneath the commissurotomy wound in the few individuals we have had who died within two weeks of operation (fig. 7).

Frictional effects are exerted by the motion of the heart valve and other portions of the heart. It is quite possible that this mechanism described by Massell, Mote and Jones may be operative following mitral commissurotomy but that the reaction is more intense because the irritant is not at a distance from but directly upon abnormal rheumatic tissue.

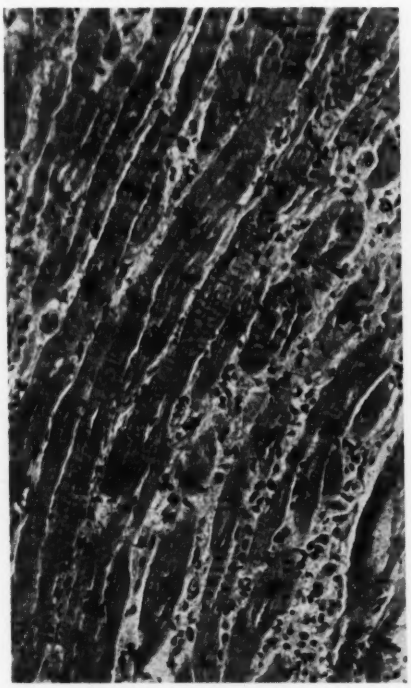

FIG. 8. Biopsy of the left auricular appendage showing nonspecific chronic inflammatory changes (200 ×).

The frequency and intensity of the pain seen in the syndrome is not apparently the usual phenomenon reported in naturally occurring rheumatic fever. We do believe, however, that pain of lesser intensity is not infrequent in adults with rheumatic activity. We were surprised, in reviewing our data, at the frequency with which a history of recurrent precordial pain occurring years before operation was obtained in this group of patients. The pain is more commonly milder and it may be that, at times, this type of pain has been attributed to psychoneurotic origin.

We have seen in an individual dead 10 days after mitral commissurotomy, in whom biopsy of the left auricular appendage showed nonspecific inflammatory cells (fig. 8), Aschoff bodies in the papillary muscles (fig. 9) and nonspecific inflammatory cells in the parietal pericardium (fig. 10) along the line of suture that were as suspicious of rheumatic activity

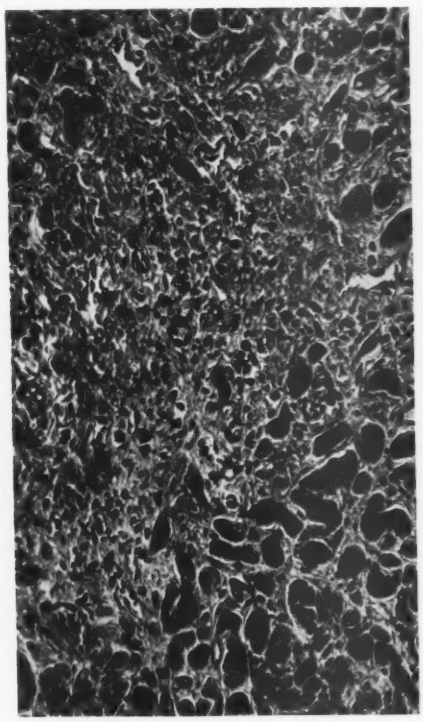

FIG. 9. Biopsy of the papillary muscle of the same heart from which the biopsy of the left auricular appendage seen in figure 8 was obtained. Note the Aschoff body (200 ×).

as were those seen in the left auricular appendage. We have seen a similar pericardial reaction in another individual, dead two weeks after operation, whose biopsy of the left auricular appendage was positive for Aschoff bodies. The greater incidence and greater severity of pain in this syndrome than that in naturally occurring clinical activation may be related to the greater involvement of the parietal pericardium.

We have not been able to correlate the

febrile syndrome following mitral commissurotomy with any event in the patient's history related to rheumatic fever or to the operative findings or to the biopsy report of the left auricular appendage. There were 15 biopsies of the left auricular appendage positive for Aschoff bodies out of a total of 37 (40.5 per cent). This percentage is practically

FIG. 10. Biopsy of the parietal pericardium of the same heart showing large blood vessels and perivascular cellular infiltration (200 ×).

identical with that of biopsies positive for Aschoff bodies in those who did not develop the postcommissurotomy syndrome. We, of course, were not surprised that the febrile syndrome occurred in some individuals with biopsies negative for Aschoff bodies because the tiny sample examined is but a small fraction of the entire heart. We have just illustrated a biopsy of the left auricular appendage negative for Aschoff bodies in a heart which contained Aschoff bodies within its papillary muscles. From these studies, we are inclined to agree with those who state that an individual with rheumatic heart disease has active rheumatic carditis through the rest of his life in the sense that a steady state of health or disease lasts as long as there is a balance between the disease-producing rheumatic agent and a healing tendency of the host. This balance can be readily upset and one method of doing so is apparently operative trauma. Perhaps, in the future, a more careful history with particular reference to the effect of all nonspecific insults on the immediate subsequent course of rheumatic heart disease may help to differentiate those individuals who will from those who will not develop the syndrome.

A discussion of the prognosis of the febrile syndrome involves a comparison with the prognosis of mitral commissurotomy in those individuals who did not develop the syndrome. The term "mitral commissurotomy" implies a uniform operative accomplishment. Unfortunately, not only is the operative accomplishment not uniform but also the operative findings before commissurotomy and a host of other factors are not uniform. We are in the process of attempting to analyze all of these factors in an attempt to evaluate the so-called functional results. For these reasons, we prefer to report our results in the following fashion that we admit is not entirely satisfactory. Of the 43 who developed the postcommissurotomy febrile syndrome, three died, four are psychotic, two developed hemiplegia and five developed permanent auricular fibrillation. Of the remaining 29, four required less medication than before operation and stated that they felt much better and were able to do much more. Eight required the same amount of medication as that required before operation and 17 required either intermittently or constantly more medication than before operation. Even in the group who required more cardiac medication following the postcommissurotomy syndrome, several stated that they felt better and were able to do more.

Finally, we believe that the incidence of this syndrome is greater than we have reported and may be closer to that of the incidence of pain that we have found. We believe this is so because (1) the incidence in those patients we have had the opportunity of following personally is higher, (2) we have seen in consultation several patients in whom fever was not recognized either because the temperature was not taken, the pain being regarded as of incisural origin, or taken incorrectly because lips were not sealed continuously while the oral temperature was taken, and (3) because several of our referring physicians are using large amounts of salicylates routinely after hospitalization, a practice that we heartily approve.

Summary and Conclusions

1. A febrile syndrome following mitral commissurotomy is described.

2. Excluding four individuals who developed an immediate precipitation of rheumatic fever, the syndrome occurred in 43 (24.0 per cent) of 179 consecutive individuals subjected to mitral commissurotomy.

3. This syndrome is characterized by the appearance of an episodic recurrence of a combination of events first occurring after a variable latent period following mitral commissurotomy and is uniformly characterized by precordial pain and fever, is frequently associated with the precipitation or intensification of heart failure and is at times accompanied by migratory joint pains, arrhythmias, hemoptysis or psychosis and sometimes terminates in death.

4. Because of the frequency of this syndrome following mitral commissurotomy and its absence following any other nonrheumatic cardiac or pulmonary surgery and because of the frequent cardiac involvement, the syndrome is regarded as a reactivation of rheumatic fever.

5. Reasons are given for believing that the incidence of this syndrome is even greater than herein reported.

Sumario Español

Un síndrome febril subsiguiente a la comisurotomía mitral se describe. El síndrome consiste de una repetición episódica de una combinación de sucesos que ocurren primeramente luego de una fase latente variable consiguiente a la comisurotomía mitral y uniformemente se caracteriza por dolor precordial y fiebre, comunmente caracterizado por la precipitación o intensificación de decompensación cardíaca previamente existente y variablemente acompañado de dolores migratorios en las coyunturas, arritmias, hemotisis o psicosis y algunas veces terminando en desenlace fatal. El síndrome se encontró ocurrir en 43 (24 por ciento) de 179 sujetos consecutivos sometidos a una comisurotomía mitral. Porque nunca hemos observado este síndrome subsiguiente a ningún otro tipo de cirugía noreumática o cirugía pulmonar y por otras razones nos vemos compulsados a considerar esto como una reactivación de la fiebre reumática.

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Antibiotic Therapy of Bacterial Endocarditis

IV. Successful Short-Term (Two Weeks) Combined Penicillin-Dihydrostreptomycin Therapy in Subacute Bacterial Endocarditis Caused by Penicillin-Sensitive Streptococci

By JOSEPH E. GERACI, M.D., AND WILLIAM J. MARTIN, M.D.

Twenty-three patients with endocarditis caused by penicillin-sensitive streptococci have received short-term treatment with penicillin and dihydrostreptomycin, combined, for two weeks. Five of the patients died from complications of their infection; 18 were living and well, at the time of this study, after an average follow-up period of more than one year. No failures in treatment or relapses have occurred. It is concluded from the study of these patients that 1,000,000 units of aqueous procaine penicillin-G and 1 Gm. of dihydrostreptomycin sulfate given intramuscularly every 12 hours for two weeks is curative for this type of endocarditis.

A PRACTICAL form of short-term therapy for subacute bacterial endocarditis would be of considerable economic and psychologic value. The importance of such short-term therapy can be appreciated if one considers the expenditure of time and money involved currently in treating a patient afflicted with the disease mentioned. In a recent paper[1] it was estimated that the average cost of present-day treatment of a private patient with subacute bacterial endocarditis, exclusive of physicians' fees, amounted to $601. If infectious endocarditis affects the breadwinner of the family so that he is without gainful employment for several months, the economic loss and consequent psychologic effects may be very distressing.

Current concepts of the therapy of bacterial endocarditis caused by penicillin-sensitive organisms indicate that the average daily dose of penicillin should be 1 to 2 million units and that treatment should be continued for four to eight weeks.[2-4] In contradistinction to this conventional duration of treatment, "short-term therapy" applies to those instances in which treatment is not given beyond two weeks. King and colleagues[5] treated eight patients with penicillin on an intensive short-term basis. Their eight patients, seven with streptococcal and one with staphylococcal subacute bacterial endocarditis caused by penicillin-sensitive organisms (sensitivity range of 0.02 to 0.3 unit with an average of 0.1 unit per cubic centimeter of medium), were treated with 14 million units of penicillin per day for 10 days. Only the patient with the most resistant organism (sensitive to 0.3 unit per cubic centimeter) was cured. In one other of their cases, therapy with both short-term massive daily doses and with long-term conventional daily doses of penicillin was without success. The organism responsible for the endocarditis was a very sensitive one, and combined therapy with penicillin and streptomycin was eventually curative.

Hamburger and Stein[6] treated 12 patients with 15 or 16 million units of penicillin given daily for two weeks. Two of these patients had a relapse within one month and were then successfully retreated with a second course. Hunter,[7, 8] encouraged by in vitro studies on the synergistic bactericidal effects of combined penicillin and streptomycin, treated five patients who had penicillin-sensitive streptococcal endocarditis with this antibiotic combination for 10 days and obtained satisfactory results.

From Jan. 1, 1951, through January, 1953, a 25-month period, we have treated 23 consecutive patients who had penicillin-sensitive streptococcal endocarditis. In these 23 cases

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combinations of penicillin and dihydrostreptomycin were given for a period of two weeks.

Material and Method

The diagnosis of bacterial endocarditis in our 23 cases was established in each instance by an average of three (range two to six) positive blood cultures. After the organism was identified and in vitro sensitivity tests carried out, the patient was given aqueous procaine penicillin G intramuscularly in a total daily amount of 1.2 to 2.4 million units; this amount was given in divided doses two, three or four times per day for 14 days. Dihydrostreptomycin sulfate was given also in a total daily amount of 1.2 to 2.4 Gm. in divided amounts either in combination with the penicillin in the same injection or as a separate injection.* Blood cultures were obtained twice a week during therapy, and several daily consecutive blood cultures were obtained after therapy was completed. Urinalyses were made and sedimentation rates were determined twice per week. Assays for the concentration of penicillin and dihydrostreptomycin were made once a week in most cases. For the penicillin assays the Fleming slide cell technic was used.[9] For the dihydrostreptomycin assays a tube dilution method using *Klebsiella pneumoniae* as the test organism was employed.

The organisms isolated were *Streptococcus mitis* in 20 cases, *Streptococcus salivarius* in two, and an unidentified streptococcus in one. The organisms were inhibited by 0.1 unit of penicillin or less per cubic centimeter in all instances save one. The unidentified streptococcus was inhibited by 0.2 unit per cubic centimeter. The in vitro antibiotic sensitivities of the isolated organisms were determined by the use of the agar-plate dilution method as described by Herrell and Heilman.[10] The results of the sensitivity tests were read at the end of 16 hours, or when organisms on the control plate with no antibiotic had grown well.†

In some cases, in vitro sensitivity studies were also made with Aureomycin, terramycin, dihydrostreptomycin, or erythromycin. In 13 cases the isolated organisms were inhibited by 0.39 to 3.1 micrograms (average 1.14) of terramycin or Aureomycin or both per cubic centimeter; none of these patients were treated with these drugs. In six cases the organisms were inhibited by less than 0.05 to 0.2 microgram (average 0.11 microgram) of erythromycin. In two cases each, the streptococci were inhibited by less than 0.05, 0.1 and 0.2 microgram of this drug; only two of these six patients were treated with erythromycin. Sensitivity studies for dihydrostreptomycin were made in only two of the cases; the values were 6.25 and 3.1 micrograms for organisms which were sensitive to less than 0.05 unit of penicillin.

In view of previously reported studies of bactericidal tests for combined penicillin-dihydrostreptomycin activity on penicillin-sensitive streptococci, such studies were not carried out with the organisms isolated in this series of patients.[8, 11-13]

Clinical Features

Sixteen of our 23 patients were men and seven were women. Their ages ranged from 26 to 66 years and averaged 45 years. Precipitating pathogenetic factors were elicited in only nine patients; in the other 14 the history did not reveal any possible source for the valvular infection. In five cases the extraction of teeth was definitely implicated and in four an upper respiratory infection or sore throat seemed to be the determining event leading to the onset of the disease. The duration of symptoms before treatment was started by us averaged three and a half months and varied from 2 to 68 weeks.

Table 1.—*Initial Symptoms Encountered in 23 Cases of Penicillin-sensitive Streptococcal Endocarditis*

Symptom	Cases
Malaise, asthenia, weakness, fatigue	10
Low-grade fever and malaise	7
Chills and high fever	4
Headache and nausea	1
Anemia	1
Acute organic toxic psychosis	1
Total	24*

* One patient had two attacks of the disease.

The onset of the disease was acute, almost dramatically sudden, in five and gradual or insidious in 18 (table 1). In four of the five cases in which the onset was acute, the sudden appearance of a chill or chills and fever was the first manifestation of the disease; in the other case the sudden onset of a severe throbbing headache was the initial symptom. In eight

* We are grateful to Eli Lilly & Company, Indianapolis, Ind., and Chas. Pfizer & Company, Inc., Brooklyn, N. Y., for supplying us with procaine penicillin G and dihydrostreptomycin sulfate combined in the same cartridge and for supplying us with combiotic.

† We are greatly indebted to Drs. Heilman, Thompson, Needham and Ulrich, of the Section of Bacteriology, Mayo Clinic, for their help in the study of these patients.

cases the patient had no previous knowledge of the presence of heart disease, in 12 the diagnosis of bacterial endocarditis had not been established before the patient came to the clinic, and in three the presence of bacterial endocarditis had been suspected at home but had not been diagnosed.

The symptoms in these cases were similar to those previously reported by other authors (table 2). In many instances a low-grade fever, malaise, anorexia, and a feeling of ill health characterized the patient's illness and were the only symptoms complained of. The presence of an associated heart murmur was the clue to the source of the patient's difficulty. Fever occurred in every case. In 13 cases the fever was of low grade all of the time and the temperature was never higher than 102 F. In nine cases the temperature on several or many occasions exceeded 102 F. and reached levels as high as 105 F. Chills occurred surprisingly often. Sweats and arthralgias were prominent features. In one case the onset of the patient's illness was accompanied by the sudden onset of a very severe pain in the left sacroiliac region. Roentgenographic study of this site revealed a destructive arthritis which was felt to be of embolic origin. Both the pain and the local changes cleared up rapidly with therapy for the endocarditis. The details of this complication will be reported in a separate communication.

TABLE 2.—*Symptoms Recorded in 23 Cases of Penicillin-sensitive Streptococcal Endocarditis Prior to Therapy*

Symptom	Cases
Fever	23
Malaise, asthenia, tiredness, weakness	22
Chills	14
Sweats	12
Arthralgia	9
Anorexia	9
Headache	7
Pallor or anemia	6
Sore throat	4
Mild cough	4
Other central nervous system symptoms	4
Mild effort dyspnea	3
Nausea	1
Diarrhea	1

Physical Findings. The physical findings in the 23 cases are listed in table 3. Definite antecedent heart disease was established clinically in 22 of the 23 patients. Rheumatic heart disease was felt to be present in 18, and degenerative or "arteriosclerotic" heart disease in three patients. In one case syphilitic heart disease with syphilitic aortic insufficiency was diagnosed and demonstrated at postmortem examination. In one case it was not possible to state whether any pre-existing heart disease was present. This patient was a 34 year old housewife in whom a minimal apical systolic murmur was present initially during therapy but was absent when she returned for reexamination one month after therapy. She had no prior knowledge of heart disease or a heart murmur.

TABLE 3.—*Physical Findings Noted in 23 Cases of Penicillin-sensitive Streptococcal Endocarditis on Admission and Prior to Treatment*

	Cases
Cardiac signs	
Heart murmurs*	23
Apical systolic	16
Aortic diastolic	8
Aortic systolic	4
Apical diastolic	0
Heart enlarged	13
Markedly†	0
Moderately	3
Slightly	10
Size normal	10
Sinus tachycardia (rate above 100)	9
Auricular fibrillation	0
Heart failure	0
Loss of weight	15
Embolic phenomena	14
Splenomegaly	12
Clubbing	9
Changes in fundus‡	4

* Some patients had more than one murmur.

† Heart of patient became markedly enlarged during therapy.

‡ Determined in 16 cases; positive findings consisted of petechiae or small hemorrhages.

Of the 3 patients with degenerative heart disease, one was a 59 year old man who gave a history of

having had a myocardial infarction 10 years prior to the development of endocarditis (case 1, table 4). He was not aware of the presence of a murmur before admission to the clinic. He had a systolic murmur at the apex which was also heard to the left of the sternum in the third intercostal space; the size of the heart was normal. It was difficult to say whether or not this murmur represented aortic stenosis, mitral insufficiency of rheumatic origin, or perhaps mitral insufficiency resulting from the previous infarction, that is, from involvement of the posterior papillary muscle by the infarction with resulting incompetence of the mitral valve.

The second patient in this category was a 66 year old man who also was without previous knowledge of a heart murmur or heart disease prior to the diagnosis of his endocarditis (case 9, table 4). A minimal aortic systolic murmur appeared during the clinic examination when the diagnosis was being established. One year later, when the patient returned for re-examination, no murmur was heard and a phonocardiogram revealed no evidence of a bruit.

The third patient was a 60 year old man who had a minimal basal aortic murmur (case 20, table 4). He also had strong clinical evidence of coronary artery disease with angina pectoris. He gave no history of a heart murmur in his youth or early adult life. The presumptive diagnosis was aortic stenosis.

It is interesting to note (table 4) that in the 18 patients thought to have rheumatic heart disease, only the murmurs compatible with mitral and aortic insufficiency and occasionally a murmur suggestive of aortic stenosis were observed. In no case was it felt that the endocarditis was engrafted on a mitral stenosis. In six of these cases there was a definite history of previous rheumatic fever, in five there was an equivocal history and in seven there was no history of rheumatic fever or its sequelae. In seven cases there was the characteristic murmur of aortic insufficiency; in four of these patients there was no history of rheumatic fever or heart murmur, while in three an apical systolic murmur was also present. In the remaining 11 patients felt to have rheumatic heart disease, only an apical systolic murmur of minimal to moderate intensity was heard; in only one of these patients was an aortic systolic murmur noted also. This aortic murmur seemed to be of the same character as the apical murmur but much less intense. A diagnosis of rheumatic mitral valvulitis was entertained in these 11 cases, and it is probable that in most of them the murmur represented mitral insufficiency.

Of the 11 cases in which a diagnosis of rheumatic mitral valvulitis was entertained, there was a definite history of rheumatic fever in four, and equivocal history in four, and no history in three. In all of these cases except one of the last-mentioned group, there was a history of a heart murmur of long duration prior to the onset of bacterial endocarditis. In the case in which the patient was without previous knowledge of a heart murmur (case 14, table 4), examination after death disclosed that involvement of the mitral valve and its chordae tendineae by previous attacks of rheumatic fever was the substrate for the bacterial endocarditis. It would seem, then, that previous damage to the mitral valve had occurred before the onset of the bacterial endocarditis in all 11 cases. However, the possibility that the bacterial infection was engrafted on a normal mitral valve in some cases cannot be excluded. Such cases have been recorded.[14] Whether some of these apical systolic murmurs may actually have represented aortic valvular lesions would be difficult to say. However, the apical location of the murmur, the previous knowledge of valvular damage, and the presence of bacterial endocarditis would indicate that the murmur was of mitral valvular origin, and the result of rheumatic mitral incompetence. The problem of differentiation of apical systolic murmurs and organic mitral insufficiency has been reviewed recently.[13]

Embolic manifestations occurred in 61 per cent of the 23 cases. Petechiae were the most frequent finding. Osler's nodes were noted in six cases.[15, 16] Janeway's spots were noted only once.[17] Splenic infarction occurred three times, and cerebral, coronary or pulmonary embolism was diagnosed in one instance each. Major arterial embolism occurred once, in the calf of the right leg.

Laboratory Data

Anemia, noted in 15 of the 23 patients, was mild in 12 and moderate in three (table 5). The values for hemoglobin ranged as low as 6.2 Gm. per 100 cc. of blood and averaged 10.3 Gm. Leukocyte and differential counts

TABLE 4.—*Pertinent Data Relative to Antibiotic Therapy in 23 Cases of Penicillin-Sensitive Streptococcal Endocarditis*

Case	Age, sex	Type of heart disease*	Weeks of symptoms before treatment	Streptococcus isolated†	Sensitivity‡	Therapy*§						Months followed	Remarks*
						Pen		DHS		Method			
						Daily	Total	Daily	Total	Pen	DHS		
1	59 M	DHD; Cor. Scl; AP; MI? AS?	12	mitis (4)	<0.1	2	28	2	28	1 q 12 hr.	1 q 12 hr.	—	History of myocardial infarction 10 years before SBE. Apical murmur result of infarction? Died at home of myocardial infarction 21 days after therapy
2	44 F	RHD; MI	4	mitis (3)	<0.05	2	28	2	28	Same	Same	4	Blood level 1 unit Pen and 4 micrograms DHS 24 hr. after last dose
3	39 F	RHD; AI; MI	12	mitis (5)	<0.1	2	28	2	28	Same	Same	4	—
4	34 F	Type? Prob. none	3	salivarius (2)	<0.05	2	28	2	28	Same	Same	5	—
5	48 M	RHD; MI	8	mitis (4)	<0.05	2	28	2	28	Same	Same	5	—
6	45 M	RHD; MI	24	mitis (6)	0.1	2.4	33.6	1.8	25.2	0.6 q 6 hr.	0.6 q 8 hr.	21	—
7	50 M	RHD; MI	16	mitis (3)	<0.05	2	28	2	28	IV	0.5 q 6 hr.	9	Erythromycin for 28 days unsuccessful before short-term Pen and DHS were curative
8	47 F	RHD; MI	10	mitis (4)	0.1	2	28	2	28	0.4, 0.6 q 6 hr.	1 q 12 hr.	9	—
9	66 M	DHD; AS?	3	salivarius (3)	0.1	1.8	25.2	1.8	25.2	0.6 q 8 hr.	0.6 q 8 hr.	12	Reinfection one year later with same organism. Cured with erythromycin, 2 Gm. a day for 2 wk. Follow-up 1 yr.
10	51 M	RHD; MI	2	mitis (2)	<0.05	1.8	25.2	2	28	0.6 q 8 hr.	1 q 12 hr.	18	—
11	41 F	RHD; AI; MI	14	mitis (2)	<0.05	2.4	33.6	2	28	0.3 q 3 hr.	1 q 12 hr.	17	Pen O used because of marked sensitivity to Pen G. See text
12	51 M	RHD; MI	18	mitis (2)	0.1	2.4	33.6	2.4	24	0.6 q 6 hr.	0.6 q 6 hr.	12	DHS given only 10 days. Pen for 14 days. Combined therapy started 4 days after Pen treatment begun

13	45 M	RHD; MI	68	unidentified (6)	0.1–0.2	5.0	100	2	35	IV	0.5 q 6 hr.	21	Treated 20 days. See text
14	32 F	RHD; MI	16	mitis (3)	<0.05	2.4	24	1.8	16.2	0.6 q 6 hr.	0.6 q 6 hr.	—	Died 11th day of treatment from cerebral embolism. Necropsy showed RHD, MI. Valve cultures negative
15	53 M	SHD; AI	8	mitis (3)	0.1	2.4	26.4	1.8	19.8	0.6 q 6 hr.	0.6 q 6 hr.	—	Died 11th day of treatment, cong. failure. Necropsy revealed SHD with AI and SBE on aortic valve with healing. No valve cultures
16	36 M	RHD; AI	22	mitis (3)	0.05	1.2–1.6	19.4	1–2	22.5	0.4 q 6 hr.	0.5 q 6 hr.	—	Death from congestive failure 10 days after treatment finished. No necropsy
17	48 M	RHD; AI	12	mitis (2)	<0.05	1.2	16.8	1.2	16.8	0.6 q 12 hr.	0.6 q 12 hr.	26	—
18	31 M	RHD; AI	16	mitis (4)	<0.05	2.4	33.6	2.4	33.6	0.6 q 6 hr.	0.6 q 6 hr.	12	Onset accompanied by destructive arthritis of left sacroiliac joint of embolic origin which cleared rapidly with treatment
19	32 F	RHD; MI	16	mitis (4)	<0.05	1.2	16.8	1.2	16.8	0.6 q 6 hr.	0.6 q 12 hr.	23	—
20	60 M	DHD; AS; Cor. Scl.; AP	14	mitis (4)	<0.05	2.4	33.6	2.4	33.6	0.6 q 6 hr.	0.6 q 6 hr.	13	Transurethral resection during therapy without rise of temperature or bacteremia
21	26 M	RHD; MI	38	mitis (3)	<0.1	2.4	48	2.4	34	0.6 q 6 hr.	0.6 q 6 hr.	18	Treated 20 days because of marked debility and loss of weight. Duration of symptoms 9+ months
22	28 M	RHD; AI; MI	14	mitis (2)	<0.1	1.2–2	24.8	1–2	24	0.6 & 1 q 12 hr.	0.6 & 1 q 12 hr.	3	—
23	30 M	RHD; AI	18	mitis (2)	0.05	2.4	33.6	1.8	25.2	0.6 q 6 hr.	0.6 q 6 hr.	—	Died of congestive failure 2 months after therapy finished. No necropsy

* Abbreviations: RHD, rheumatic heart disease; SHD, syphilitic heart disease; DHD, degenerative heart disease; AP, angina pectoris; Cor. Scl., coronary sclerosis; MI, mitral insufficiency; AI, aortic insufficiency; AS, aortic stenosis; SBE, subacute bacterial endocarditis; Pen, penicillin; DHS, dihydrostreptomycin; IV, continuous intravenous drip; q, every.

† Numbers in parentheses represent positive blood cultures.

‡ In vitro sensitivity to penicillin in the indicated concentration (units per cubic centimeter). See text for in vitro sensitivity values for other antibiotics.

§ Numbers represent millions of units of penicillin and grams of dihydrostreptomycin given intramuscularly except where otherwise stated.

were abnormal in only a few cases. The highest leukocyte count noted on admission was 16,800 per cubic millimeter, and this was the only reading above 15,000. Reticuloendothelial cells without evidence of phagocytosis, phagocytic reticuloendothelial cells, and phagocytic monocytes without reticuloendothelial cells were noted in four cases, 2 cases and one case, respectively, of the 15 cases in which this examination was carried out. These figures are somewhat lower than were found by Cole.[18] The sedimentation rates (Westergren method)

TABLE 5.—*Significant Laboratory Data Obtained on Admission in 23 Cases of Penicillin-Sensitive Streptococcal Endocarditis*

	Cases
Anemia (hemoglobin less than 12 Gm., erythrocytes less than 4 million)	15
Leukocytosis (neutrophils more than 10,000)	4
Leukopenia (neutrophils less than 5,000)	4
Differential count (20 cases)	
Neutrophils more than 80 per cent	5
Normal	15
Blood smears (15 cases)	
Reticuloendothelial cells without phagocytosis	4
Phagocytic reticuloendothelial cells	2
Phagocytic monocytes	1
Elevated sedimentation rate (above 30)	21*
Erythrocytes persistently in urine	9
Increased blood urea (on basis of 18 cases)	3

* In the other 2 cases the rates were 20 and 23 mm. respectively.

ranged from 30 to 70 mm. in 1 hour in 12 cases, and from 71 to 100 in seven cases; in two cases the rates were greater than 100 mm., and also in two cases the rates could be considered normal. Persistent hematuria was noted in only nine cases. Roentgenograms were interpreted as showing some enlargement of the heart in only 13 cases.

RESULTS OF TREATMENT

In this series of 23 cases there were five deaths, giving a mortality rate of 22 per cent. Eighteen patients (78 per cent) have remained in good health during follow-up periods varying from 3 to 24 months. The average follow-up period was one year. No treatment failures and no relapses have occurred in the living patients. In 21 of the 23 cases the response to treatment was good and prompt. The temperature fell to normal on the day of, or the day following, the start of therapy, and continued normal throughout the remainder of the period of treatment except for an occasional brief febrile response arising from embolization. The blood cultures promptly reverted to negative and remained so during therapy and the follow-up period. In one case a low-grade fever persisted for 12 days while the blood cultures were persistently negative. In another case the initial temperature of 103 F., noted before the onset of therapy, gradually fell to normal over a four-day period. Follow-up studies of the living patients have revealed little or no change in their exercise tolerance and little or no change in cardiac size or auscultatory findings.

Deaths. Data on the five patients who died are given in table 6. It will be noted that in the three cases in which the cause of death was congestive heart failure the underlying valvular lesion was aortic insufficiency. Postmortem examinations were obtained (at the clinic) in two cases in which death occurred on the eleventh day of therapy and in a third case in which death occurred (at home) three weeks after treatment had been concluded. Cultures were obtained from the involved valves in only one of the three cases, and the results of these were negative. A résumé of the two cases in which necropsy was performed at the clinic follows.

A 32 year old white woman (case 14, table 6) gave a history of chronic febrile illness of four months' duration. Her disease had a gradual onset about a week following the extraction of several teeth. The initial symptoms of a "cold," dry cough, fever and anorexia were followed by the appearance of the nephrotic syndrome about 10 days later which lasted for approximately two weeks. The patient then had intermittent hematuria, weakness and tiredness, recurrent febrile episodes with the temperature rising as high as 104 F. and loss of weight until admission to the clinic.

Examination revealed a normal-sized heart with a moderately loud apical systolic murmur, sinus tachycardia, mild clubbing of the fingers, and splenomegaly. The laboratory findings were:

moderate anemia, leukopenia, phagocytic reticuloendothelial cells in the peripheral blood smear, elevated sedimentation rate, microhematuria, increased concentration of blood urea, and three blood cultures positive for *Streptococcus mitis*.

Therapy was complicated by the appearance of moderately severe epigastric pain on the third day, which was followed by enlargement and tenderness of the liver, jaundice, and elevation of temperature to 100.6 F. This episode lasted about four days. The patient was then afebrile and the blood cultures were negative until death, which resulted from cerebral embolism with massive infarction and hemorrhage into the left frontotemporoparietal lobes of the brain on the eleventh day of treatment.

Necropsy revealed a normal-sized heart weighing 315 Gm. The chordae tendineae were slightly thickened and shortened. The mitral valve was the only one involved. At the posterior medial commissure and in the adjacent portions of the anterior and posterior leaflets of the mitral valve, there was an erosive lesion involving the valvular tissue. This caused a moderate excavation of the involved tissue. Small thrombi were deposited upon the surface of the lesion.

Microscopic examination of the mitral valve at the site of involvement showed the remnant of valvular tissue. This was thickened by vascular fibrous tissue in which cells, predominately macrophages, were present in moderate numbers. Hemosiderin granules were present in some of these infiltrating cells. No neutrophils, leukocytes or bacteria were identified histologically. On the surface of the involved portion of the valve, endothelial cells could be identified. Bland thrombotic material was deposited upon the surface of the valve but no evidence of active inflammation could be found. Cultures from the involved portions of the leaflets were negative (figs. 1 and 2).

It was concluded that the mitral valve was the site of healed bacterial endocarditis.

TABLE 6.—*Deaths in 23 Cases of Penicillin-Sensitive Streptococcal Endocarditis*

Case	Age, sex	Type of heart disease	Duration of symptoms before treatment, months	Death		Necropsy data
				Days after treatment started	Cause	
1	59 M	Degenerative; cor. sclerosis, angina pectoris; mitral insuff. (?); aortic stenosis (?)	3	35	Coronary occlusion with myocardial infarction	Coronary occlusion. No other data from home physician
14	32 F	Rheumatic; mitral insuff.	4+	11	Cerebral embolism	Normal-sized heart. Rheumatic h. dis. with mitral insuff. Healed subacute bact. endocar., mitral valve. Cultures of involved valves negative
15*	53 M	Syphilitic; aortic insuff.	2+	11	Congestive failure	Syphilitic aortitis with syphilitic h. dis. and aortic insuff.; subacute bact. endocard., aortic valve
16	36 M	Rheumatic; aortic insuff.	5+	24	Congestive failure	—
23	30 M	Rheumatic; aortic insuff.	4+	75	Congestive failure	—

* To be reported in detail elsewhere.

The second patient (case 15,* table 4) was a 53 year old white man, whose first symptoms of bacterial endocarditis appeared to be the visual, auditory and paranoidal delusions of an acute organic toxic psychosis of some two or three months' duration. The history regarding the symptoms of his valvular infection was difficult to elicit. A diagnosis of syphilitic heart disease with aortic insufficiency had been made three years earlier. The patient had been treated for congestive heart failure in the interim between this diagnosis and his final illness. Examination revealed enlargement of the heart, an aortic diastolic murmur which indicated free aortic regurgitation, and splenomegaly. The laboratory

* To be reported in greater detail in a separate communication.

findings of significance were: moderate anemia, phagocytic reticuloendothelial cells in the peripheral blood smear, greatly elevated blood sedimentation rate (116 to 131), microhematuria, blood flocculation reaction for syphilis positive on several occasions, and blood cultures positive for *Streptococcus mitis* on five occasions. The patient died rather suddenly on the eleventh day of therapy. During the last two or three days before death he experienced several episodes of thoracic pain and dyspnea that were suggestive of pulmonary or coronary embolization.

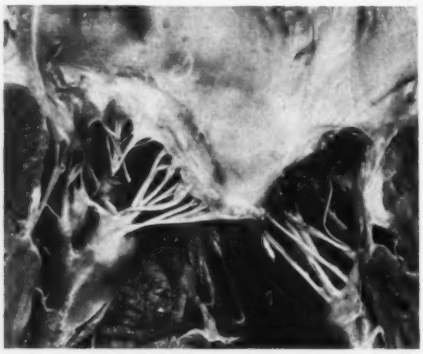

FIG. 1. Case 14. *a*. Mitral valve showing erosion in the vicinity of the posteromedial commissure and deposition of thrombi on the surface of the altered portion of the valve.

Postmortem examination revealed syphilitic aortitis and valvulitis. The heart was enlarged, weighing 610 Gm. (normal 315 Gm.), and there was considerable left ventricular hypertrophy. The coronary arteries appeared to be normal. Scattered throughout the myocardium, particularly in the left ventricle, were many 1 to 2 mm. areas of redness and softening that represented small focal myocardial infarctions. The mitral, tricuspid and pulmonary valves were normal. The thoracic aorta was unusually wide. At the aortic valve, widening of the commissures and narrowing of the ostia of the coronary arteries were readily apparent. In addition, friable gray-brown vegetations were deposited on the luminal aspect of the aortic valve. These were concentrated at the commissure between the right and posterior leaflets, at the commissure between the posterior and left leaflets, and on the left aortic leaflet.

Microscopic examination of representative lesions showed that the vegetations were composed of fibrin and colonies of cocci. Similar organisms in large numbers were present within the valvular tissue, which simultaneously was the site of necrosis with abscess formation and fibroblastic proliferation associated with ingrowth of capillaries (figs. 3 and 4).

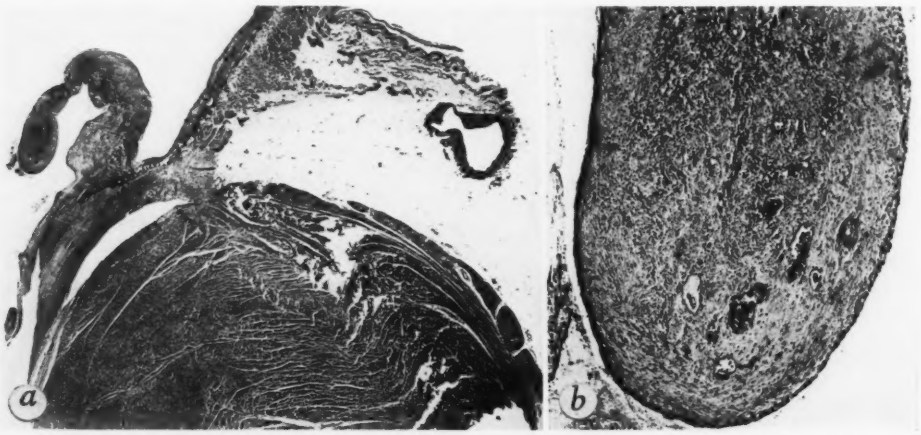

FIG. 2. Case 14. *a*. Left atrium and ventricle and posterior leaflet of the mitral valve through the involved portion shown in figure 1. The leaflet is short and thickened (hematoxylin and eosin; ×5.5). *b*. Distal portion of the mitral leaflet shown in *a*. There are thickening of the valve by vascular fibrous tissue and infiltration with macrophages, giving the picture of healed bacterial endocarditis (hematoxylin and eosin; ×50).

In the thoracic aorta there were stellate medial scarring, perivascular lymphocytic infiltration of the adventitia, and intimal atherosclerosis.

The pathologic picture was that of an unusual combination of syphilitic aortitis and bacterial endocarditis of the aortic valve. On histologic grounds, the endocarditis appeared active, with destructive and acute inflammatory features

existing. On morphologic grounds it is impossible to state whether the bacteria observed had been viable or not at the time of the patient's death. Unfortunately, cultures of the valve were not obtained.

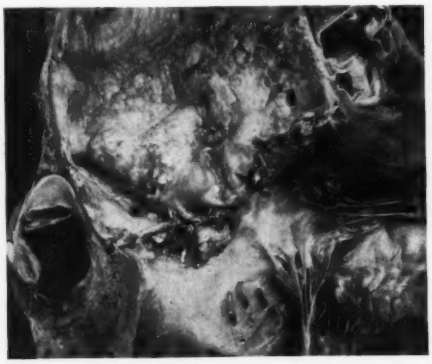

FIG. 3. Case 15. Aortic valve showing the gross characteristics of syphilitic aortitis and of bacterial endocarditis.

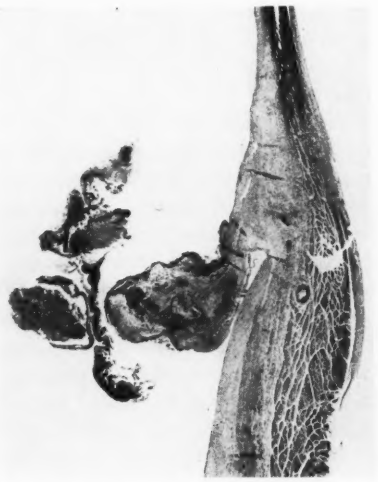

FIG. 4. Case 15. Aortic valve showing vegetations which, through artefact, have come away from the surface of the cusp. The cusp is thickened by the presence of bacteria and the cellular infiltration described in the text (hematoxylin and eosin; ×4.5).

Other Data.

In 2 of the 23 cases the period of therapy was 20 days (table 4). A longer period of treatment and a larger daily dose of penicillin in one of these two cases were decided upon for the following reasons: the organism was an unidentified streptococcus, and the in vitro sensitivity test revealed that minimal inhibition of the organism was produced by 0.1 to 0.2 unit of penicillin per cubic centimeter of medium; also, the duration of symptoms was felt to be close to 18 months; in addition, the patient exhibited considerable debility and loss of weight. In the other case the patient had had the disease for nine months or more and was in a greatly debilitated and wasted state when therapy was started. In this case a splenic infarction also developed on the third day of treatment with a rise of temperature to 103.8 F. for 48 hours. However, the initial response to therapy in both cases was excellent, and it seems likely in retrospect that 2 million units of penicillin and 2 Gm. of dihydrostreptomycin per day for 14 days would have been adequate.

In three cases (cases 7, 8 and 10, table 4) penicillin-sensitive streptococcal endocarditis had also occurred three, four and five years respectively prior to the episodes of endocarditis recorded herein. Conventional therapy with penicillin alone for 30, 42 and 23 days respectively had effected a cure in each instance; daily doses of 1, 0.6 and 0.4 million units of penicillin were given respectively. In an additional case (case 9, table 4) a reinfection occurred one year after cure with short-term combined penicillin-dihydrostreptomycin therapy; *Streptococcus salivarius* was isolated in each instance, and the sensitivity to penicillin was the same on both occasions. However, on the second occasion the organism was sensitive to less than 0.05 microgram of erythromycin per cubic centimeter of medium, and it was decided to treat the patient with this new drug.[16, 19] A half gram of erythromycin was given every six hours for two weeks. All subsequent cultures have been negative and the patient has remained well.

In one other case (case 7, table 4) erythromycin was used. The organism isolated was *Streptococcus mitis* which was sensitive to less than 0.05 unit of penicillin and to 0.2 microgram of erythromycin per cubic centimeter of medium. This constituted a reinfection endo-

carditis some three years after an initial infection. A half gram of erythromycin was given every six hours for four weeks. The initial response to treatment was excellent. The temperature dropped from 102 F. to 97 F. in a period of 12 hours and remained normal until the twenty-third day of treatment. The blood cultures rapidly became negative in the same period and remained negative until low-grade fever reappeared 23 days later. The streptococci isolated at this time were found to have the same sensitivity to penicillin, that is, they were sensitive to less than 0.05 unit per cubic centimeter of medium but the organisms were highly resistant to erythromycin, not being inhibited by more than 200 micrograms per cubic centimeter of medium. The patient was then treated with combined penicillin and dihydrostreptomycin on a short-term basis (two weeks). Two million units of aqueous crystalline penicillin G by continuous intravenous drip (the patient requested intravenous therapy) and 2 Gm. of dihydrostreptomycin sulfate in divided doses of 0.5 Gm. every six hours was given over a 24-hour period. The temperature and blood cultures again promptly became normal, and the patient made an uneventful recovery. It should be noted that during therapy with erythromycin, blood levels ranged from 2 to 16 micrograms per cubic centimeter of medium and averaged 7 micrograms. The blood levels of erythromycin in this case throughout most of the period of therapy with this antibiotic were 10 or more times greater than the amount of drug found to inhibit the organism in vitro.

As can be seen in table 4, various dosage schedules were employed. The last six patients (cases 1 to 5 and 7) have been given 1 million units of procaine penicillin G and 1 Gm. of dihydrostreptomycin sulfate every 12 hours as separate intramuscular injections, since there has been, so far, no preparation available with both these amounts of antibiotics in the same cartridge. These slightly different dosage schedules have given the same results.

The patients in this study were not asked to take their temperature after therapy was completed. However, in two cases in which a low-grade fever (temperature up to 102 F.) was observed in the first few days after dismissal of the patient, the febrile reactions were apparently not due to a relapse or reactivity of the valvular infection. Daily blood cultures during and subsequent to the elevation of temperature were repeatedly negative. The febrile response disappeared rapidly with rest in bed, and it was felt to be related to ambulation and activity following two to three weeks of almost complete rest in bed during the period of treatment and observation.

Bio-assays for the serum levels of penicillin and dihydrostreptomycin were performed in 14 cases. In 13 of these there was no evidence of renal insufficiency and the penicillin levels ranged from 1 to 16 units and averaged just above 2 units per cubic centimeter. The dihydrostreptomycin levels ranged from 4 to 64 micrograms and averaged slightly more than 16 micrograms. In one case in which the levels of blood urea averaged more than 80 mg. per 100 cc., the values for penicillin and dihydrostreptomycin in the serum were, on two occasions, 8 and 16 units per cubic centimeter for penicillin and 32 and 64 micrograms per cubic centimeter for dihydrostreptomycin. In the patients without renal insufficiency who received 2 million units of penicillin and 2 Gm. of dihydrostreptomycin per day intramuscularly in two divided doses every 12 hours, the serum levels were noted to be as high as 16 units and 64 micrograms and as low as 1 unit and 4 micrograms respectively. The higher values for penicillin and dihydrostreptomycin were found an hour or two after the administration of the antibiotics; the lower values were found one to two hours before the injections.

Sedimentation Rate.

The sedimentation rate was elevated before therapy in all but two cases, and it became elevated also in these with treatment. During therapy the sedimentation rate rose rather than fell in a significant number of cases. In 13 cases it rose an average of 25 mm., the range being from 10 to 56 mm.; the initial readings in these cases averaged 60 mm. with a range of 20 to 84 mm. In only two cases were the rises correlated with embolic phenomena or an observable change in the patients'

clinical status. In both instances rises of 41 and 56 mm. were associated with splenic infarction and a corresponding febrile reaction.

In six cases the sedimentation rate remained grossly unaltered, and during therapy it did not rise or fall more than 10 mm. The average initial readings in these cases ranged from 23 to 123 mm. with an average of 62 mm. In only four cases did the sedimentation rate fall with therapy. The average fall was 24 mm. with a range of 10 to 38 mm. The initial readings in these cases averaged 78 mm. and ranged from 40 to 136 mm.

In 19 cases the initial sedimentation rates were as high as or higher than the readings obtained at completion of therapy. In most cases the values had decreased to normal when the patients were re-examined after a month or two. A rise in the sedimentation rate has been noted also with the therapy of other types of bacterial endocarditis. One can only speculate on the significance of these findings.

Comment

For practical clinical and therapeutic consideration, cases of subacute streptococcal endocarditis can be divided into two large groups: those in which the organism is penicillin sensitive and those in which it is penicillin resistant. In the first category are the cases of subacute bacterial endocarditis caused by streptococci such as *Streptococcus mitis*, *Streptococcus salivarius*, and related organisms. These streptococci have been found to be uniformly sensitive to penicillin; occasionally one is encountered which is resistant to penicillin particularly when much previous unsuccessful penicillin therapy has been given.[4, 20-22] Penicillin-resistant streptoccal endocarditis is rather uniformly caused by the enterococci, most commonly *Streptococcus faecalis*. We have not been concerned with the latter patients in this paper, since long-term combined penicillin-dihydrostreptomycin therapy for six weeks with large daily doses of penicillin is usually indicated in such cases.[8, 23] Enterococcal endocarditis will be considered in a separate communication.

Patients with penicillin-sensitive streptococcal endocarditis have in the past made up the bulk of most series of those with this infection; the proportion has been variable but has run as high as 80 to 90 per cent or more of the cases. In recent years, with the widespread use of penicillin and broad-spectrum antibiotics, this proportion seems to have dropped to figures closer to 60 per cent.[8, 20, 24] This decrease in penicillin-sensitive streptococcal endocarditis seems to be an absolute one and also seems to be related to the widespread use of penicillin and other antibiotics in patients with any and all types of fever regardless of cause. That this may be so is illustrated by a case encountered recently at postmortem observation at the clinic and reported below, and by other patients seen at the clinic.

In January 1947, a 60 year old man came to the Mayo Clinic because of low-grade fever and malaise. A presumptive diagnosis of lymphoblastoma was made after repeated blood cultures were negative; x-ray therapy was given over the liver and spleen, since these organs were enlarged. A month later the patient returned because of increasing malaise, anorexia, loss of energy and strength, fever, and chills. The admission temperature was 104.8 F. Many blood cultures were negative after two days of incubation. On the sixth day of hospitalization, treatment with penicillin was given empirically; 120,000 units were administered daily for the first three days and then 320,000 units a day for the next seven days, for a total of 2.6 million units for the 10 days. The temperature fell to normal on the fourth day of treatment, and was still normal at the time of dismissal 19 days later. Only one of the many blood cultures obtained before the onset of therapy became positive—an anaerobic streptococcus was grown after 12 days of incubation. Many blood cultures obtained after therapy was started were negative. Six months later the patient began to have symptoms of congestive heart failure. Improvement followed conventional therapy. Bouts of congestive heart failure then recurred for the next four years until death supervened. Postmortem examination revealed organic mitral insufficiency with a healed mitral bacterial endocarditis.

The foregoing case illustrates the ease with which penicillin-sensitive streptoccal endocarditis can be cured in some cases, and the very small doses of penicillin that may be curative. There must be many similar cases in which fever is the chief manifestation of bacterial endocarditis and in which cure is obtained without a definite diagnosis being made

prior to treatment. This case is to be contrasted with that reported by King and colleagues,[5] in which both short-term treatment (10 days) with daily massive doses of penicillin and long-term treatment (six weeks) with conventional daily doses of penicillin were without success for a very penicillin-sensitive streptococcal endocarditis (organism inhibited by 0.02 unit of penicillin per centimeter of medium). Combined therapy with penicillin and streptomycin was curative. These two cases illustrate the relative extremes of therapy that may be curative for penicillin-sensitive streptococcal endocarditis, and indicate the difficulty that is encountered occasionally in the treatment of such patients.

A number of in vitro studies have been carried out relative to the synergistic effect of penicillin and dihydrostreptomycin on penicillin-sensitive *Streptoccus viridans* organisms. Hunter[8] studied the effects of a combination of penicillin and dihydrostreptomycin on several strains of penicillin-sensitive viridans streptococci in vitro and found enhanced bactericidal activity. Spicer[25] studied six strains and found that the combination of antibiotics had a greater bactericidal action than did penicillin alone on two of the organisms and the same effect as did penicillin alone on four others. Spicer,[25] Spicer and Blitz,[11] and Eagle[26] have noted that even when sensitive strains of streptococci are studied in vitro with large doses of penicillin, a residue of viable organisms remains. These organisms were killed when exposed to streptomycin.[11, 25] Jawetz[12] has also studied several penicillin-sensitive strains of *Streptococcus viridans* for synergism and noted this effect in a number of instances. The efficacy of this antibiotic combination or penicillin-sensitive viridans streptococci has been further demonstrated in vivo by scattered reports of cases in which penicillin alone in adequate dosage for a prolonged period resulted in failure, but cure occurred when streptomycin was used together with penicillin.[5, 27] It would seem that penicillin and streptomycin in combination have a greater bactericidal effect than penicillin alone for most strains of penicillin-sensitive viridans streptococci, having either a more rapid and greater killing effect or only a greater killing effect on the organisms. In all instances the combination seems to be as effective as penicillin alone; no instance of antagonism has been recorded when this combination has been used against these organisms.

Further study of these penicillin-sensitive streptococci for antibiotic synergism between penicillin and streptomycin and other antibiotic combinations is indicated. Further observation and combined antibiotic treatment of patients with penicillin-sensitive streptococcal endocarditis may indicate that an even shorter period of therapy, of 10 days' duration, as suggested by Hunter,[7, 8] may be adequate. Because of the greater bactericidal effect of the penicillin-dihydrostreptomycin combination against these sensitive streptococci, further in vitro and clinical experience may perhaps show that daily doses of 2 million units of penicillin, as suggested herein, or larger doses, with or without benemid, together with dihydrostreptomycin may be curative for a shorter period of time, such as one week. Only further clinical study will reveal what is the optimal ideal therapy for these patients.

Increasing experience by others[8] and our own observations in the antibiotic therapy of bacterial endocarditis indicate that combined therapy is being used in an increasingly greater percentage of all cases, particularly for infections resistant to penicillin and other individual antibiotics. Whether combination treatment will mean a shortening of the period of therapy in types of endocarditis other than those due to penicillin-sensitive streptococci can be determined only by further study and experience. Further in vitro testing, in vivo animal experiments and the actual treatment of the disease in man with combinations of antibiotics will eventually clarify this highly fascinating problem in the field of antibiotic therapy. In vitro and in vivo testing for antibiotic synergism with combinations of antibiotics will assume an ever-increasing importance in the management of bacterial endocarditis, especially in those cases in which the infection is caused by antibiotic-resistant organisms.

The average duration of the valvular in-

fection in our 23 cases was very close to four months. This seems to be a surprisingly long time when one considers that these patients had symptoms and considered themselves ill all of this time. In view of the availability of very effective antibiotic therapy for patients with penicillin-sensitive streptococcal endocarditis, it is interesting to speculate on what the therapeutic results and the percentage of living patients would have been in this series had the diagnosis of infectious endocarditis been made in the early weeks of the disease.

The major problem today is not so much the actual antibiotic treatment and the control of the infection as the making of an early accurate diagnosis. By this we mean the isolation and proper identification of the etiologic organism and the reliable determination of in vitro sensitivity. It is well known that active bacterial endocarditis of many months' duration leads to much valvular damage which in turn compromises cardiac function and leads to the complication of congestive heart failure, the most frequent cause of death in such cases.[28]

In all five cases in which death occurred in our series the disease had been present for several months (table 6). In case 15 it is likely that the disease was present for a much longer period than the recorded two months. In this case the onset and history of the disease were obscured by the presence of an organic toxic psychosis apparently of endocarditic origin. Thus it seems probable that the complications of the endocarditis causing death in these cases might not have occurred if an early diagnosis had been made and early adequate antibiotic therapy had been given. In the two cases in which death occurred on the eleventh day of the disease and in which postmortem examination was carried out at the clinic, there was considerable healing of the valvular lesions.

The evidence from this clinical study indicates that penicillin-sensitive streptococcal endocarditis is completely controlled by the short-term treatment described. It seems reasonable to conclude that early diagnosis should result in cure of the infection and ensure a living patient in 100 per cent of cases except when prolonged active valvular infection from delay in diagnosis or when previous extensive cardiac damage leads to congestive heart failure, cerebral embolism or renal insufficiency.

In only three cases of this series did any toxic reactions develop from the antibiotics used, and these reactions were mild. One patient gave a history of severe allergic sensitivity to penicillin G, so that penicillin O was used for the two-week period of therapy. Cross sensitivity must have existed, because a maculopapular rash developed over most of the areas of the body with eventual exfoliation of the skin of the fingers and hands. Successful two-week curative therapy was, however, carried out with penicillin O and dihydrostreptomycin. This case has been reported in greater detail elsewhere.[29] Two patients exhibited very mild toxic reactions to dihydrostreptomycin. One had a slight transient numbness of the fingertips following the first few injections of dihydrostreptomycin; the other had numbness and paresthesias circumorally and peripherally in the tips of the fingers and toes which persisted unchanged with continuation of treatment until death from cerebral embolism on the eleventh day. No eighth-nerve toxicity from the dihydrostreptomycin was exhibited by any of the 23 patients given this drug in 2 Gm. doses for a two-week period.

Summary and Conclusions

Twenty-three consecutive patients with penicillin-sensitive streptococcal endocarditis seen during a 25 month period have been treated with a combination of penicillin and dihydrostreptomycin on a short-term basis (two weeks). Eighteen patients (78 per cent) have remained well during follow-up periods of 3 to 24 months. No treatment failures or relapses have occurred in the living patients.

Five deaths (22 per cent) occurred. Four of the deaths were due to complications of the endocarditis and the underlying heart disease, namely congestive heart failure and cerebral embolism, while the fifth was due to coronary occlusion with myocardial infarction.

The clinical features in the 23 cases are presented and the cardiac findings discussed. Rheumatic heart disease was present in 18 cases, degenerative or "arteriosclerotic" heart

disease in three, and syphilitic heart disease with syphilitic aortic insufficiency in one; in one case no diagnosis of underlying heart disease could be made.

It is concluded on the basis of this study that 1 million units of aqueous procaine penicillin G and 1 Gm. of dihydrostreptomycin sulfate given intramuscularly every 12 hours for two weeks represents adequate and curative treatment for subacute bacterial endocarditis caused by penicillin-sensitive streptococci.

Sumario Español

A veinte y tres pacientes con endocarditis causada por estreptococos penicilino-sensitivos se le dió un tratamiento corto de dos semanas con penicilina y dihidroestreptomicina. Cinco de los pacientes murieron a consequencia de complicaciones de la infección; 18 aún vivían y mantenían buen estado de salud hasta la fecha de este estudio luego de un tiempo promedio de vigilancia de más de un año. No ocurrieron fracasos en el tratamiento o recaídas. Se concluye de el estudio de estos pacientes que 1,000,000 de unidades de procaína penicilina-G acuosa y 1 gramo de sulfato de dihidroestreptomicina administrado intramuscularmente cada 12 horas por dos semanas es curativo para esta variedad de endocarditis.

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The Relation of Age to Certain Electrocardiographic Responses of Normal Adults to a Standardized Exercise

By HAROLD M. SILVER, M.D., AND MILTON LANDOWNE, M.D.

To demonstrate what may be expected in individuals who do not show clinical evidences of heart disease, the authors present a quantitative evaluation and physiologic interpretation of data obtained from 60 male subjects. Age differences are described. Decreases in S-T and in T occurred in most subjects. The S-T depression is not necessarily ascribable to injury, and no discontinuity of distribution is discovered to justify calling any of the observed responses "abnormal." The results emphasize the limitations to interpretation of information which is not highly specific, in subject material where no primary standard of diagnosis has been established.

EXERCISE provides a commonly encountered increase in cardiac work load, and has been considered a useful tool in the study of the cardiovascular system. For the clinician who appreciates that cardiovascular disease may exist despite normal findings in the patient at rest, exercise may uncover signs, both clinical and electrocardiographic, of an otherwise nonevident disorder. Criteria have been proposed for the judgment of an abnormal electrocardiographic response to exercise, a judgment which may govern important medical and social decisions. There is some difference of opinion as to the best criteria to use.

The purpose of the present study is to provide systematic data in subjects up to 80 years of age and to contribute to the background upon which rational criteria for clinical evaluation may be based. A careful selection of "normal" subjects was made. The authors are aware that the standards which formed the basis for selection were to some extent arbitrary and, in addition, admit to ordinary clinical fallibility. Using conventional clinical electrocardiographic technics, the authors present and analyze some of the responses to a standard exercise.

In the studies which perhaps have been most widely used as exercise tests of physical fitness, Schneider[1] based normal performance on observations of young adults. Master and Oppenheimer,[2, 3] considering their test as a measure of cardiac function, adjusted the work load for age, weight and height to equalize the response of systolic blood pressure and heart rate. Their extensive series includes only three male subjects (less than 2 per cent) over the age of 59 years. When the clinical usefulness of the test was extended by including the electrocardiogram,[4, 6] the same and double the amounts of work were used. On the basis of a considerable prior clinical experience, these authors had already formulated[4, 5] an estimate of what constituted an abnormal electrocardiographic response, and had given these criteria as part of their procedure. They reported[6] that none of 58 normal males between 40 and 68 years of age showed a "positive test," in contrast to one third of 136 patients with coronary artery disease. Quantitative measurements of the responses were not included in this paper. A recently reported series from Master's laboratory[7] justifies and more satisfactorily defines the response considered as abnormal, since this occurred in only 6.5 per cent of subjects judged clinically normal. The incidence of "abnormal" response was not consistently different with age, but in this report their oldest subject was 57.

Among the many reports which deal with the electrocardiographic effects of exercise in relation to the diagnosis of heart disease, only

From the Section on Gerontology, National Heart Institute, National Institutes of Health, Public Health Service, Federal Security Administration, Bethesda, and the Baltimore City Hospitals, Baltimore, Md.

few[8-12] include the performances of "normal" individuals above the age of 60. In these, the total number of older subjects was low, and an evaluation of the effect of age difference was not undertaken.

Studies directed primarily toward the evaluation of age differences are few. Heier[13] compared 32 subjects who were 65 to 85 years of age and clinically free of heart disease with a control group between 20 and 30 years of age. Although less exercise was performed, 18 instances of T-wave change were noted in the old group; diminution occurred in eight of these. No alterations were observed in his young group. Herve and Santander[14] studied 30 normal subjects of various ages. They reported changes in T_{II} after Master's exercise text in 14 of 20 subjects below the age of 30, as compared to two of seven subjects between 40 and 56 years. S-T depression occurred frequently without difference related to age. Mazer and Reisinger[15] tested two groups of 44 male subjects, mean ages 28 and 46; the oldest subject was 56 years old. Each subject climbed two 9 inch steps as many times as he could in one and one-half minutes. The mean performance of the older group was 35.2 trips, which was 85 per cent that of the younger group. The total work was comparable with that which we have used, and to the "double Master's" test, but was performed at twice the rate. Records which were taken "within three minutes after the end of exercise" were analyzed, and revealed a significant diminution from control in T in lead I, and elevation in II, III and CF_4. The change which occurred was not significantly different in the two age groups. Depression of S-T exceeding 0.75 mm. occurred in 80 per cent of the older subjects and 32 per cent of the younger. Barrow and Ouer[16] noted the effects of uncontrolled vigorous exercise in two age groups of 50 subjects each (mean ages 31 and 49). Changes of T wave occurred most frequently in leads III and CF_4 in both groups; in 72 per cent of the group 21 to 40 years old, and in 58 per cent of the group 41 to 67 years old. The magnitude and direction of the change was not specified. Savilahti,[17] including subjects with cardiac disease in his older group, detected no effect of age on the Q-T changes induced by exercise.

Materials and Methods

Sixty male subjects divided into three equal groups covering the age spans 20 to 39, 40 to 59, 60 to 79 years, were selected after a careful evaluation to exclude clinically detectable cardiovascular disorders. Attention was paid to all the details which contemporary rigorous clinical authority requires.* The aged subjects, selected largely from the Gerontology Section or from the Infirmary Division of the Baltimore City Hospitals, were active and ambulatory. The other groups were drawn from the staff of the Gerontology Section and from patients on the surgical service prior to elective surgery, who had no special athletic training or conditioning. Mean ages for the groups were 31, 48 and 67 years.

Clinical evaluation was made by one examiner (H. M. S.) with intent to exclude. The criteria for selection included a careful history and physical examination which disclosed no evidence of cardiac disease; diastolic blood pressure not more than 90 mm. Hg; teleroentgenographic transverse cardiac diameter not more than ±15 per cent of normal values for height and weight[18]; 12 lead electrocardiogram judged not definitely abnormal using the criteria of Burch and Winsor[19] except that no exclusion was made on the basis of Q-T duration; and hemoglobin (Sahli) above 12 Gm. per 100 cc. Because of these stringent criteria the old subjects represent a select group, from which many an able-bodied candidate was excluded.

The test procedure consisted of walking in cadence for three minutes over two steps. The subject lifted himself 18 inches (0.46 meters) each trip. The number of trips for each subject was calculated to yield a total work of 660 kilogram-meters per square meter of body surface area.† A one and one-half minute practice was done at least four hours prior to the test; there was no other training. Standard, augmented unipolar limb and precordial leads V_2, V_4, V_5 and V_6 (from electrodes strapped to the chest) were recorded on a four-channel direct writing electrocardiographic machine (Sanborn Polyviso), at a recording speed of 25 mm per second constant in any record to ± .002 second; and carefully stand-

* Understandably an exercise or anoxia test could not be used as a means of selection.

† The number of trips was readily calculated from weight in Kg. (W) and standard tables for surface area in square meters (S), as $\frac{600}{.46}$ or $1300\,\frac{S}{W}$. Since these surface area tables are based on height in cm. (H) and weight, the calculation basically becomes

$$9.4\,\frac{H^{.725}}{W^{.675}}.$$

ardized to a sensitivity of 1 mv. = 10 mm. Records taken with the subject recumbent were obtained before exercise, immediately (0 minutes) and 2, 4, 6 and 10 minutes after the end of exercise. At least six cycles were recorded, and all 10 leads were taken as rapidly as possible, so that records were completed within 30 seconds after the designated time. In addition, after one and one-half minutes of exercise in 42 subjects and at two and one-half minutes in all subjects, records were taken of V_2 and V_4 for measurement of R-R (cycle length) and Q-T, the subject standing at rest for 10 seconds at these times.

Individual values of R-R and Q-T were obtained by averaging six cycles, three each from leads V_2 and V_4, measured to the nearest 0.01 second. Maximum T-wave height and S-T level were measured to the nearest ¼ mm. in three complexes in each lead and averaged. For these measurements the P-Q interval was used as reference level. Polarity follows conventional notation except that aV_R is presented as minus aV_R, for purposes of consistency. Derived measures such as $Q\text{-}T_c = \frac{Q\text{-}T}{\sqrt{R\text{-}R}}$, or the changes in any value, were calculated for each individual subject. The resulting values are expressed in seconds and in millimeters (1/10 mv.), or in quarters of millimeters (1/40 mv.).

The mean values and the standard deviations of the distributions (σ_d) of R-R, Q-T and T are presented. These values are expressed to the nearest significant figure. Because S-T frequency distributions were asymmetric, they have been tabulated in terms of the median values, and the extremes encountered are detailed. A t test was used to compare two means. For estimation of the significance of an age difference among the three age groups an F test was employed. Probability values (p) were assigned to the t scores and to the variance ratios for R-R, T, and Q-T data. The term "significant" indicates that the estimated probability (p) of chance difference is equal to or less than 0.02; "highly significant," less than 0.01. Age differences in the time course of T-wave means were evaluated by an F test of the age by time interaction based on the five records taken after exercise. Significance was assigned to p values ≤ 0.01, and for highly significant differences $p \leq 0.001$. Correlation was tested by correlation coefficient (r) for linear correlation of ungrouped data.

Results

Work

On the basis of their body size (surface area) all subjects performed the same work. The total calculated work for each individual averaged 1088 kilogram-meters, with a range of 935 to 1295. Since the mean weight of the subjects in our groupings decreased slightly with age, the mean work for the oldest group was almost 5 per cent less than the over-all mean. Because subjects with large calculated surface area generally weighed more, they performed more work per trip. As a result there is less variation in the number of trips than in the work performed. The average number of trips was the same, or 35, for each age group and the range for individuals was from 30 to 40.

Table 1.—*The Effect of Age and Exercise on Heart Rate (Mean Cycle Length in Seconds)*

	Control	Exercise 2½ min.	After Exercise				
			0 min.	2 min.	4 min.	6 min.	10 min
Young							
Mean	.87	.53	.66	.86	.85	.85	.85
σ_d*	.13	.07	.09	.13	.14	.13	.14
t score†			10.2	0.6	1.5		
Middle							
Mean	.83	.53	.63	.83	.82	.80	.80
σ_d*	.12	.07	.08	.13	.12	.11	.12
t score†			10.6	0.3	0.9		
Old							
Mean	.84	.52	.58	.75	.78	.78	.79
σ_d*	.12	.09	.11	.16	.14	.13	.13
t score†			15.1	3.9	4.3	4.5	4.5
All							
Mean	.85	.53	.62	.82	.81	.81	.81
σ_d*	.12	.07	.10	.15	.13	.13	.13
F ratio‡	0.6		3.3	3.4	1.6		

* σ_d = Standard deviation of the distribution.

† Comparison with control; $t \geq 2.5$ indicates a statistically significant ($p \leq .02$) cardioacceleration.

‡ A ratio of less than 4.2 does not indicate significant age difference in R-R.

Rate

Mean cycle length (R-R) for each age group was very nearly the same before exercise, and after two and one-half minutes of exercise decreased to the same degree (by about 40 per cent) in each group (table 1). (This also applies to the observations at one and one-half minutes of exercise.) Recovery was slower in the old group, where the mean R-R remained

significantly below control level until after 10 minutes, while significant cardioacceleration was evident in the younger two groups only in the records taken immediately after exercise. The difference in rate of recovery was suggested in the shorter average cycle length for the old group immediately after exercise, but significant age difference in R-R was not demonstrable at any time. Variability of R-R was the same in all groups at rest, and decreased during exercise. At two minutes of recovery the oldest group showed the greatest variability.

S-T

Selection of subjects with normal electrocardiograms restricted the range of control values for S-T and T. Age differences in control S-T levels were slight. In all leads except V_4, median values in each age group were no more than ¼ mm. from the reference level. In V_4, the median value was ½ mm. for the two younger groups, and ¼ mm. for the old group (table 2). A tendency toward a relative lowering of S-T with age may be noted in the slightly lower median values for the oldest group in $-AV_R$, aV_F, V_2, V_4, V_5, V_6. The selection of subjects placed a minimal limit on S-T, and minimal values for each group were $-¼$ mm., except for one young subject who showed a depression of ¾ mm. in lead II and one old subject with a depression of ½ mm. in V_5. Exercise generally resulted in slight depression of the S-T level (elevation in aV_R), usually maximal immediately after exercise, and most evident in V_4. *F* ratios were computed for selected leads to test whether observed differences in means could be attributed to age grouping. These ratios were all low for the control period, and considerably higher immediately after exercise (table 2) indicating that exercise consistently increased differences attributable to age.*

The *maximal recorded S-T change at any time* was ascertained for each subject. The median value for this maximal change in all 60 subjects was ½ mm. in V_4, ¼ mm. in II, aV_F, V_5 and V_6 and less than ¼ mm. in the remaining leads. The median for the old group was larger than one or both of the younger groups in all leads except III, aV_L and V_2. The largest individual change was recorded in an elderly subject whose S-T was lowered by 1¾ mm. in lead II, 1½ mm. in V_2, 1¼ mm. in V_5 and 1 mm. in V_4. In all but three subjects the recorded S-T change was less than 1½ mm. Four of the five subjects exhibiting a change greater than 1 mm. were in the old group. In eight subjects (two young, three middle and three old) a maximum change of 1 mm. was recorded, occurring twice in lead II, five times in V_4 and three times in V_5.

Recovery was evident at two minutes after the completion of exercise, and by four minutes only two subjects (one middle, one old) showed changes from control of more than ½ mm. in the limb leads. In the chest leads, changes exceeding 1 mm. persisted in one subject (old), while a change of 1 mm. remained in three subjects (one young, two old).

The *lowest level of S-T attained* was influenced in part by the control level, but more by the amount of change. A resultant maximal depression of S-T to more than ½ mm. below reference level was recorded in 11 subjects, eight of whom were in the old group. The greatest depression was $-1¾$ mm. in one case. No subject evidenced an S-T level lower than -1 mm. in the limb leads, and only two subjects, both elderly, exceeded this lower limit in the chest leads.

T-Wave Height

Despite factors of case selection, mean control T height decreased slightly with age in all leads except III, but the differences were significant only in lead I. In the majority of leads (I, II, aV_R, V_4, V_5, V_6) reduction in mean T height was evident immediately after exercise (table 3, fig. 1). In the young and middle groups partial recovery was noted two minutes later, while in the oldest group mean values continued to decrease to a minimum at four minutes. The maximum recorded change (table 3) was largest in V_4, and in all precordial leads was greatest in the oldest group. This maximum change was recorded latest in aV_F and V_2, and in all leads was latest for the

* Because the S-T data do not have a normal distribution, probability (*p*) values are not assigned to these *F* ratios.

TABLE 2.—*The Effect of Age and Exercise on S-T Level (Median Values and Extremes in Quarters of Millimeters: 1 unit = 0.025 mv.)*

Lead		Control				After Exercise								
						0 minutes			4 Minutes			Greatest recorded decrease		
		Min.	5%*	Med.	Max.	Min.	5%*	Med.	Min.	5%*	Med.	Med.	95%†	Max.
$-aV_R$	Young	−1	0	0	2	−1	0	0	−1	0	0	0	2	2
	Middle	0	0	½	2	0	0	0	0	0	0	0	2	2
	Old	0	0	½	2	−3	−1	0	−1	−1	0	1	2	4
	All	−1	0	0	2	−3	−1	0	−1	0	0	½	2	4
aV_F	Young	−1	0	1	2	−1	0	0	−1	0	0	0	2	2
	Middle	−1	0	0	4	−2	−1	0	−1	−1	0	1	2	2
	Old	0	0	0	2	−2	−2	0	−1	−1	0	1	2	2
	All	−1	0	0	4	−2	−1	0	−1	−1	0	1	2	2
I	Young	0	0	0	2	−1	0	0	0	0	0	0	1	1
	Middle	0	0	0	2	−1	0	0	−1	0	0	½	2	2
	Old	−1	0	0	2	−1	−1	0	−1	0	0	1	2	2
	All	−1	0	0	2	−1	−1	0	−1	0	0	½	2	2
II	Young	−3	0	0	2	−3	−2	0	−4	0	0	½	3	4
	Middle	−1	0	1	4	−3	−2	0	−1	0	0	1	3	4
	Old	−1	−1	0	3	−4	−4	−1	−3	−2	0	2	5	7
	All	−3	−1	0	4	−4	−4	0	−4	−1	0	1	4	7
	F ratio‡		0.5				4.0			1.6				
V_2	Young	0	0	0	7	0	0	½	0	0	0	0	1	2
	Middle	0	0	0	6	0	0	0	0	0	0	0	2	2
	Old	−1	0	−½	8	0	0	0	−1	0	0	0	4	6
	All	−1	0	0	8	0	0	0	−1	0	0	0	4	6
	F ratio‡		0.3				2.8			1.1				
V_4	Young	0	0	2	8	−1	−1	0	0	0	2	1½	3	4
	Middle	−1	0	2	6	−2	−1	0	−1	0	1	1½	4	6
	Old	−1	0	1	4	−6	−4	−1½	−5	−3	0	2½	5	6
	All	−1	0	2	8	−6	−3	0	−5	−1	½	2	5	6
	F ratio‡		1.4				10.0			10.8				
V_5	Young	−1	0	1	6	−1	0	0	−1	−1	½	1	4	4
	Middle	0	0	0	5	−3	−2	0	−2	−1	0	1½	4	4
	Old	−2	−1	0	3	−7	−6	−½	−7	−3	0	2	5	5
	All	−2	0	0	6	−7	−3	0	−7	−1	0	1	4	5
	F ratio‡		1.8				6.6			4.6				
V_6	Young	−1	0	1	3	0	0	0	0	0	1	1	2	2
	Middle	0	0	1	4	−1	−1	0	0	0	0	1	3	4
	Old	0	0	½	2	−3	−3	0	−2	−2	0	2	3	4
	All	−1	0	1	4	−3	−2	0	−2	0	0	1	3	4
	F ratio‡		1.3				6.2			6.3				

* 95 per cent were this value or higher.

† 95 per cent were this value or less.

‡ Indicates the ratio of variation about the mean assignable to age to the remaining variation; the higher the ratio the greater the indication of an age effect. A ratio less than 4.2 does not suggest significance.

TABLE 3.—*The Effect of Age and Exercise on T-Wave Height (Mean Values in Millimeters; 1 mm. = 0.1 mv.)*

Lead	Subjects	Control		After Exercise						
				0 Min.		4 Min.		Maximum change		
		Mn. mm.	σ_d‡ mm.	Mn. mm.	σ_d mm.	Mn. mm.	σ_d mm.	Mn. mm.	σ_d mm.	Time§ min.
$-aV_R$	Young	2.6	(.5)	2.2	(.6)	2.5	(.5)	0.5	(.3)	1
	Middle	2.3	(.7)	1.7	(.5)	2.1	(.7)	0.7	(.5)	1
	Old	2.1	(.8)	1.8	(.5)	1.7	(.5)	0.6	(.5)	2
	All ages	2.3	(.7)	1.9	(.8)	2.1	(.6)	0.6	(.5)	1
	F ratio	3.1		4.6*		9.7†				
aV_F	Young	2.4	(.8)	2.1	(.8)	2.2	(.9)	0.5	(.3)	2
	Middle	2.0	(.7)	1.8	(.7)	1.7	(.6)	0.4	(.4)	1
	Old	2.1	(1.0)	2.0	(.8)	1.7	(.9)	0.6	(.4)	3
	All ages	2.2	(.8)	2.0	(.8)	1.9	(.8)	0.5	(.4)	2
	F ratio	1.1				1.6				
I	Young	2.4	(.8)	1.8	(.7)	2.3	(.8)	0.7	(.4)	1
	Middle	1.9	(.7)	1.2	(.5)	1.8	(.7)	0.7	(.5)	0
	Old	1.8	(.7)	1.2	(.4)	1.3	(.6)	0.7	(.3)	2
	All ages	2.0	(.8)	1.4	(.6)	1.8	(.8)	0.7	(.4)	1
	F ratio	4.3*		7.9†		10.5†				
II	Young	3.2	(.8)	2.1	(.8)	2.9	(.8)	1.1	(.6)	0
	Middle	2.9	(.8)	2.0	(.8)	2.5	(.7)	0.9	(.8)	0
	Old	2.8	(1.0)	2.2	(.7)	2.2	(.8)	0.9	(.6)	2
	All ages	3.0	(.8)	2.1	(.8)	2.5	(.8)	1.0	(.7)	1
	F ratio	1.1		0.1		5.0†				
V_2	Young	6.3	(3.5)	6.5	(2.9)	5.8	(3.5)	1.0	(1.5)	2
	Middle	6.1	(2.3)	5.8	(2.6)	5.6	(2.4)	1.1	(1.6)	2
	Old	6.0	(3.5)	4.9	(2.6)	4.3	(2.7)	2.2	(2.0)	3
	All ages	6.1	(3.1)	5.7	(2.7)	5.3	(2.9)	1.4	(1.4)	2
	F ratio	0.1		1.7		1.7				
V_4	Young	7.9	(2.8)	6.3	(2.4)	7.4	(2.7)	1.7	(1.2)	1
	Middle	6.8	(2.5)	5.2	(2.4)	6.3	(2.6)	1.8	(1.3)	1
	Old	5.9	(3.3)	4.7	(2.1)	4.3	(2.8)	2.0	(1.7)	3
	All ages	6.8	(3.0)	5.4	(2.3)	6.0	(2.9)	1.8	(1.5)	1
	F ratio	2.4		2.5		6.7†				
V_5	Young	5.3	(1.6)	4.1	(1.5)	4.9	(1.7)	1.3	(.9)	1
	Middle	4.8	(1.8)	3.6	(1.5)	4.1	(1.9)	1.4	(.8)	1
	Old	4.1	(1.8)	3.5	(1.2)	2.8	(1.4)	1.6	(1.1)	3
	All ages	4.7	(1.8)	3.7	(1.4)	3.9	(1.8)	1.4	(.9)	2
	F ratio	2.2		1.1		8.9†				

continued

TABLE 3.—*Continued*

Lead	Subjects	Control		After Exercise						
				0 Min.		4 Min.		Maximum change		
		Mn. mm.	σ_d‡ mm.	Mn. mm.	σ_d mm.	Mn. mm.	σ_d mm.	Mn. mm.	σ_d mm.	Time§ min.
V_6	Young	3.4	(1.0)	2.7	(1.0)	3.1	(.9)	0.8	(.6)	1
	Middle	2.9	(1.2)	2.2	(1.1)	2.6	(1.1)	0.8	(.5)	0
	Old	2.7	(1.0)	2.1	(.8)	1.9	(.8)	1.1	(.6)	2
	All ages	3.0	(1.1)	2.3	(1.0)	2.5	(1.1)	0.9	(.6)	1
	F ratio	2.3		1.7		8.2†				

* $F \geq 4.2$ is significant ($p \leq .02$).
† $F \geq 5.0$ is highly significant ($p \leq .01$).
‡ σ_d = standard deviation of the distribution, $\sigma_m = \sigma_d \times .022$.
§ average, to nearest minute.

oldest group. Because of this development pattern a highly significant age difference in T height was manifest immediately after exercise only in lead I (which showed a difference before exercise), but by four minutes after exercise highly significant age differences were found in leads II, aV_R, V_4, V_5 and V_6 as well as in I. Changes in III and aV_L were, as with S-T, not well displayed. In V_2 mean values decreased to a minimum at two minutes in all three groups. The change was greater for the old group, but the age difference is not assigned statistical significance. None of the T waves became isoelectric or inverted (except for leads aV_L and III). Changes in any particular lead which were more than twice the standard deviation beyond the average maximal change for that lead for all subjects occurred in three "young," three "middle" and four "old" subjects. The maximum individual change in the limb leads was 3 mm. In the precordial leads three subjects showed a change exceeding 5 mm. The subjects who had relatively large T-wave changes usually exhibited these in more than one lead.

Variability of T was not consistently altered with age, and only slightly lessened after exercise. Due to the diminution in T height with age and after exercise, the coefficient of variability was often higher in the oldest group, and generally increased with exercise. Both the standard deviation and the coefficient of variability of the maximum change in T were least in lead I.

Q-T

Prior to exercise, mean Q-T was slightly longer in the oldest group, but the agewise difference was not statistically significant ($F = 1.25$). After two and one-half minutes of exercise, Q-T showed mean decreases of 0.066, 0.067 second and 0.085 second for the young, middle, and old groups respectively, a significant agewise effect of exercise ($F = 5.01$, $p < 0.01$). Early recovery proceeded at approximately the same rate in all age groups, so that the difference in average Q-T shortening persisted at two minutes. In the oldest group the resting Q-T occupied a greater proportion of the cycle length, and although significant age differences were not evident in R-R or in Q-T at rest, the inversely directed trends are emphasized in the relative duration of electrical systole $Q\text{-}T/\sqrt{R\text{-}R}$, which manifests a significant age increment ($F = 4.29$, $p = 0.02$). Cardioacceleration during exercise was not associated with equivalent shortening in Q-T, so that the proportion of the cycle occupied by electrical systole rose at one and one-half and two and one-half minutes of exercise. This was more evident in the two younger groups, because of the initial relatively greater Q-T length in the old. When calculated as $Q\text{-}T/\sqrt{R\text{-}R}$, no increase is shown for the mean of the old group during exercise. The delayed R-R recovery in the oldest group was paralleled by recovery of Q-T, while the more prompt recovery of R-R in the younger groups reduced

the relative duration of electrical systole below control levels until after two minutes.

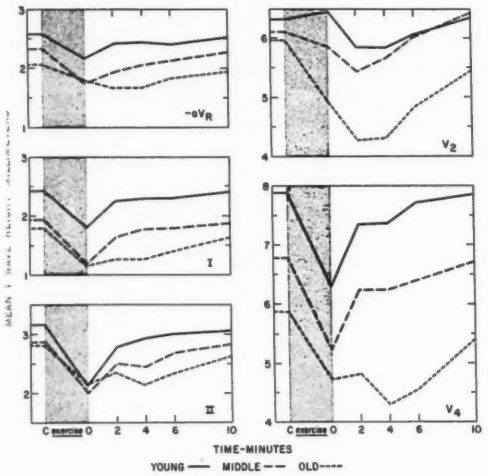

FIG. 1. The effect of age and standard exercise on mean T-wave height.

TABLE 4.—*The Effect of Age and Exercise on the Q-T Interval (Mean Value in Seconds)*

	Control	During Exercise (2½ min.)	After Exercise				
			0 min.	2 min.	4 min.	6 min.	10 min.
Young	.381	.315	.327	.377	.380	.382	.382
Middle	.375	.308	.317	.369	.375	.374	.373
Old	.390	.305	.319	.369	.379	.382	.386
F ratio	1.25	1.08					

DISCUSSION

I. Control or Resting Data

This material presents values for S-T and T which are within normal limits as reported in the literature. Mean values for T in the precordial leads are higher than those cited for younger normal subjects,[20, 21] or for a group over 60 years of age.[22] Means for the standard limb leads and unipolar limb leads in subjects up to 60 years correspond, but our values for the old subjects exceed other published means.[22] Since subjects were excluded from our series if their electrocardiograms were abnormal, our material is essentially predefined, and is not suited to the purpose of establishing electrocardiographic norms. The demonstration of age differences within this material, therefore, is more meaningful. Although we anticipate a higher incidence of coronary arteriosclerosis in clinically normal subjects after the age of 40, the average degree of involvement in our subjects may be expected to level off at the sixth decade.[23] The age decrement in T height appears in those leads whose approximate axes of derivation make small angles with the major axis of T. Since some of the lead axes lie on either side of the major T axis, the general diminution in these scalars suggests that a primary decrease in the recorded vector magnitude with age might have been found if appropriate vector technics had been employed. Age effects of change in tissue conductivity are not excluded however. The slight decrease in ratio of mean values for I/aV_F, or aV_R/II implies a minor rotation toward the right in spatial orientation. Of the 10 leads recorded, leads III, aV_L and V_2 provide little information about changes in magnitude, as they are placed at angles disadvantageously nearer to 90 degrees with the major T axis than are the other leads. In this situation, however, they are sensitive to change in position of the electrical axis. Mean control values for Q-T, particularly for the old group (0.39 second), were longer than average reported values,[19, 24 fig. 55] but within normal limits by these standards, and by standards for the aged.[17, 22]

II. Effects of Exercise

The equality in average rate during exercise may be taken to indicate that either equal, or unequal but supramaximal, stimuli to heart rate were provided, with equal maximal rate responses. The delay in recovery for the older subjects would indicate either a reduced performance in response to an equal load, or the imposition of a greater cardiac work load by the exercise, or both. Rate recovery cannot be compared with Master's normals[1, 2] since he used a one and one-half minute test to establish his normal recovery time of two minutes or less. Recovery time in our subjects was comparable to that found in normal young

subjects tested at similar work levels by Straumann.[25]

Exercise served to develop the latent electrocardiographic differences between the age groups, increasing and making significant preexisting differences in means. In no situation was a greater similarity found after exercise than before, indicating that the multiple effects of exercise on S-T and T do not cancel out existing or provoked differences. Systematic measurements of QRS were not made, but Q-T was shortened. Prolongation of QRS relative to Q-T has been asserted to explain the S-T depression of exercise,[24, page 259] and this would be consonant with the greater depression of S-T and reduction of Q-T in the older group. Although the largest S-T and R-R changes occurred over the same period of time, no correlation exists between the magnitudes of these changes ($r = .04$), so that the degree of cardioacceleration is not an index of the amount of S-T displacement. The ultimate basis for a depression in S-T level is assignable to one or more of three causes: (1) altered time pattern of activation, (2) faster return of activity curve in one region relative to another, or (3) development of regions of altered polarization pattern in deeper muscle layers which persist during the resting state, that is, "injury" potentials. We have no factual evidence as to the relative roles of these factors. The rapid evolution of S-T changes suggests that transient alterations are normally responsible. It does not appear necessary to ascribe these changes to injury unless they are more protracted, or are unrelated to the expected changes in synchronization. The slightly more evident S-T depression in the older group does not warrant the assumption of mechanisms qualitatively different from those operative in young subjects. While these data are compatible with an anticipated limitation of myocardial circulation in old subjects, they can neither prove nor disprove such an hypothesis. Since the test provides multiple factors capable of producing S-T changes, it would be fallacious to conclude that the changes noted are de facto the result of injury.

The general decrease in T height in most leads after exercise is interpreted to indicate a diminution in the vectorial magnitude of T. In the old group particularly, this continued to develop after exercise was over. Smaller decreases in the middle and young groups were accompanied by changes indicative of transient rotation of the T vector to the right and anteriorly immediately after exercise. Mean increases in T_{II} and T_{III} did not occur. Lepeshkin[24] summarizes numerous studies on the effects of exercise on T waves, describing at least three phases. A primary reduction has been recorded during and immediately following mild exercise, yielding to elevation if the exercise is strenuous or prolonged. Such elevation may continue to develop after exercise is over, and declines in two to three minutes. In the normal individual and particularly in untrained subjects, a secondary depression is described, evident three to five minutes after the end of exercise, especially in leads II and III. Straumann[25] emphasized that work load, time after exercise, and body position are all important determinants of the amount of T-wave change. Using a computed T vector, he described a reduction in the primary and an increase in the secondary T depression, as work in the supine position was increased. Sherlis[7] as well as others have commented that the displacement resulting from the "double Master's" test was usually, but not invariably, greater than that found by the "single" test. Our results, like those of Straumann, indicate that where comparative observations are being made, it is important to consider the time after exercise at which records are taken. Because of the variation in the time at which maximal change may occur, a relationship between work load and maximal displacement may not become apparent unless continuous records are obtained.

The age differences in time course of T depression noted in the means for our three age groups were highly significant in leads aV_R and V_5 ($F = 6.52, 6.76$; $p < 0.001$). When the time courses of S-T and of T are compared, it is noted that the evolution of T level after exercise finds a correspondence in S-T for the young group, but not for the oldest subjects, where greater decrease in T continues during S-T recovery. Thus for a given manifes-

tation of initial alteration in S-T, the processes restoring a normal repolarization pattern are delayed in the older subjects. A difference in the pattern of ventricular gradient change is thereby suggested.

The changes in Q-T with exercise exemplify the lag noted in the adaptation of Q-T to sudden changes in heart rate.[24, 26] Since rate recovery for the oldest group was not as prompt, this "hysteresis" of Q-T is not evoked after exercise in this group.

Summary and Conclusions

A standardized exercise was administered to 60 males 20 to 80 years of age who were selected as evidencing no clinical cardiovascular disease. The rate of work performed was adjusted for body size but not for age.

Some of the resulting electrocardiographic alterations are described and analyzed. Findings common to the three age groups studied were depression of S-T appearing promptly and most evidently in leads V_4, V_5, V_6 and II. Considering any lead, the maximal change of S-T was less than 1½ mm. in all but three subjects, or in 95 per cent of the material. By four minutes after exercise, a change of more than 1 mm. in the precordial leads was exhibited by only one subject, and a change of more than ½ mm. in the limb leads persisted in two subjects.

A decrease in T height was evident in the majority of recorded leads, and tended to become maximal during the course of the recovery period. The mean of the maximal change in T was greatest in V_4, with a value of -1.8 mm. and a standard deviation of distribution of ± 1.5 mm. The maximum recorded individual decrease in T of the limb leads was 3 mm. in lead II. In the precordial leads a decrease of more than 5 mm. occurred in three cases. Isoelectric or inverted T waves did not occur (excluding aV_L and III). The few subjects with relatively large T-wave changes usually exhibited these in more than one lead.

Within the general pattern of response, age differences were noted. The oldest group evidenced comparatively delayed recovery of heart rate, and greater reduction in Q-T during and immediately after exercise. A greater depression of S-T, and diminution of T occurred with age. The evolution of T-wave change was relatively delayed in the oldest group with maximal decreases in T occurring later in the recovery period.

Acknowledgments

Mr. Raymond Flath deserves credit for the efficiency with which technically suitable records were obtained, and Mr. Jesse Yaffa gave valuable assistance in computation. The authors are also indebted to Dr. M. Halperin, for instruction and assistance in the statistical aspects of the study.

Sumario Español

Para demostrar lo que se puede esperar en individuos que no muestran evidencia de enfermedad cardíaca, los autores presentan una evaluación cuantitativa e interpretación fisiológica de los datos obtenidos en 60 sujetos hombres. Diferencias en edad se describen. Decrementos en ST y en T ocurrieron en la mayoría de los sujetos. La depresión en ST no es necesariamente atribuíble a daño y ninguna descontinuidad de distribución se descubrió para justificar las respuestas obtenidas "anormales." Los resultados recalcan las limitaciones de interpretación de información no altamente específica en material donde no se ha establecido una pauta primordial de diagnóstico.

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Age Changes in Heart Rate and Blood Pressure Responses to Tilting and Standardized Exercise

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Tilting and standardized exercise caused extensive shifts of heart rate and auscultatory blood pressures in 140 ambulatory male subjects from 20 to 92 years of age. Following similar exercise, the older subjects showed a greater increase of heart rate and pulse pressure than did the younger subjects who compensated the changes caused by tilting more completely and rapidly than did the older subjects. These slower compensatory responses of older subjects should be considered in the interpretation of metabolic recovery rates after exercise.

TILTING and step-test exercise have been used often as cardiovascular stress situations and included in tests of the ability of the human subject to make proper hemodynamic adjustments.[1-4]

Certain questions have arisen in connection with the interpretation of (1) the results of treadmill or other exercise experiments in which the subject undergoes a change in posture between the exercise and the recovery period, and (2) age data gathered from experiments where old and young subjects were stimulated by different levels of stress.

A change in posture would seem to introduce a large cardiovascular component into the recovery pattern of cardiovascular and metabolism measurements following stress situations, although, such change might not interfere with the estimation of an over-all metabolic effect.

Everyday tasks confronting older people are essentially the same as those confronting young people except where special allowance is made for age. Individual differences make it difficult to equalize stress for subjects of various ages by relating the stress to age, weight, height, surface area, or other individual characteristics.

In order to understand better the effects of posture and age, experiments were performed to answer the following questions:

1. What changes in heart rate and blood pressure occur after tilting human subjects (feet down) to 45 degrees and to the standing position? Are there age differences in these changes?

2. What age differences occur in heart rate and blood pressure responses to exercise which is standardized for all subjects with respect both to rate and to total amount?

METHODS

Subjects. The subjects tested were 140 ambulatory male patients, employees, and staff members of the Baltimore City Hospitals between 20 and 92 years of age. The only requirement was the ability to perform the exercise.

Design. Each subject was tested once according to the following schedule: At zero time subjects reclined on the tilt table in the horizontal position. A standard blood pressure cuff and a stethoscope pickup were then fitted to the right arm. The heart sounds were recorded continuously from a transducer with low-frequency response. Measurements of systolic and diastolic blood pressure were started at nine minutes after zero time and read on the same schedule for all subjects.

Subjects were tilted feet down to 45 degrees at 15 minutes, returned to horizontal at 25 minutes, tilted to standing at 35 minutes, and sat in a straight chair at 41 minutes. They stood at 47 minutes and exercised until 48.5 minutes, when they again sat in the chair until 56.5 minutes. The exercise was performed by walking over two 9 inch steps (total height, 18 inches) the number of times required by each subject to perform 222 kilogram-meters (S.D. dist. = 16 Kg.M.) of work in the 1.5 minutes al-

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lowed. Support to the subject was provided by a foot-board and the table in all positions of tilt.

Blood pressures were read at 30-second intervals for four minutes after tilt and exercise. The first reading was taken 15 seconds after change in position. Heart rates were counted from the record over 15-second intervals and were measured for each 15-second interval for two minutes after tilts and for three minutes after exercise.

Treatment of the data. Mean values by age decades were computed for each measurement (systolic blood pressure, diastolic blood pressure and heart rate) at each time interval and plotted against time. An analysis of variance was used to assess the statistical significance of differences observed in the average curves. For the analysis, the total variance was partitioned as shown in table 2.

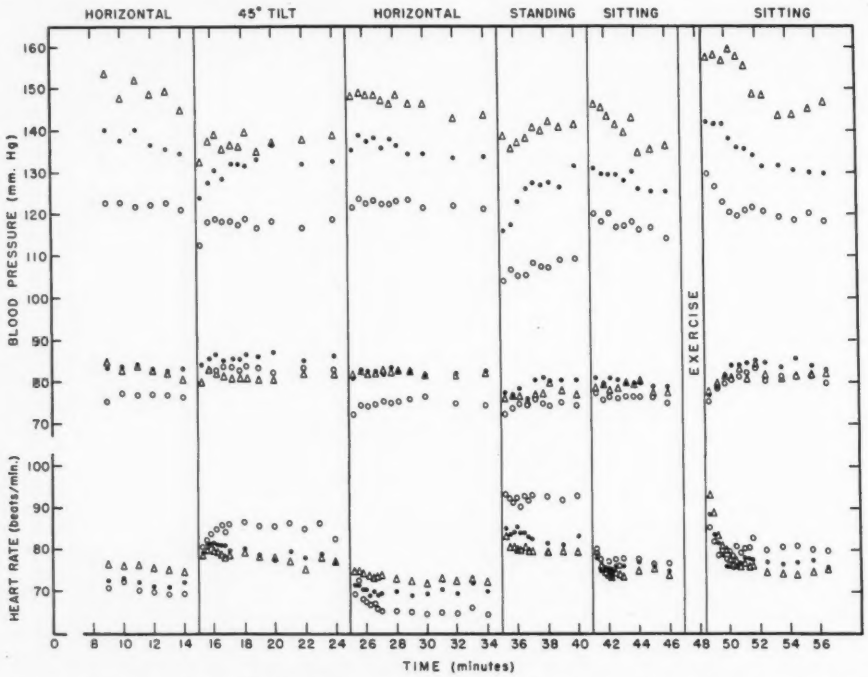

FIG. 1. Systolic and diastolic blood pressure (mm. Hg) and heart rate (beats per min.) are plotted against time (minutes) for three age groups: 20–29 year, ○; 60–69 year, ●; and 80–92 year, △. Vertical lines indicate exact time of change in position. Positions are indicated at the top of the figure. Exercise was performed in the standing position.

RESULTS

Figure 1 shows for three of the age groups (20–29 years, 60–69 years, 80–92 years) the average values of systolic blood pressure, diastolic blood pressure, and heart rate plotted against time after the beginning of the experiment.

Although the instantaneous values for heart rate and blood pressure upon tilting or at the end of exercise cannot be determined with the methods used here, the direction of these shifts can be estimated from the slope of the curve following the readings taken 15 seconds after change in position or after exercise (fig 1). Table 1 shows the direction of these shifts in heart rate and blood pressure for each change in position. The directions of these shifts, if any, were the same for all age groups.

From figure 1 it may be seen that mean systolic blood pressure levels were higher in the older subjects than in the young, while diastolic blood pressure and heart rate levels were similar for both old and young.

Following tilt to 45 degrees, older subjects showed a greater drop and a slower return of

systolic blood pressure levels than did the young, while diastolic blood pressure levels remained unchanged. Also, after this tilt, the heart rate increased more in the young subjects than in the old.

Following tilt to the standing position the systolic blood pressure decreased similarly* in both old and young subjects, while the diastolic blood pressure levels show a greater drop and slower recovery in the old subjects than in the young. Also, after tilt to standing, the heart rate increased more in the young subjects than in the old.

TABLE 1.—*Direction of Blood Pressure and Heart Rate Responses to Change in Position*

Position Change	Systolic B.P.	Diastolic B.P.	Heart Rate
From horizontal to 45° tilt	decrease	no change	increase
From horizontal to standing	decrease	decrease	increase
From 45° tilt to horizontal	increase	decrease	decrease
From standing to sitting	increase	no change	decrease
From standing exercise to sitting	increase	no change	increase

Comparison of observations taken with the subject, *sitting after standing*, and *sitting after exercise in the standing position*, shows that:

1. Older subjects increased their systolic blood pressure levels more after exercise, and returned to pre-exercise levels later than did the young.

2. There were no age differences in diastolic blood pressure responses after exercise.

3. After exercise the heart rate increased more and reached postexercise levels later in the old than in the young subjects.

For a quantitative verification of the above conclusions, an analysis of variance was applied to the first nine blood pressure readings and the first 11 heart rate estimates made after tilt to 45 degrees, tilt to standing, sitting after standing, and sitting after exercise in the standing position. The two tilts were compared as were the two conditions of sitting. The results of these analyses are summarized in table 2. Variance ratios were taken as indicating significant primary effects or interaction effects when $p < 0.05$. Asterisks indicate ratios significant with $p < 0.001$.

These analyses indicate that after tilting and exercise there is a significant age difference in levels of systolic blood pressure (age effect, systolic blood pressure),* but no significant age difference in diastolic blood pressure or heart rate levels (age effect, diastolic blood pressure, heart rate). Further, individuals can be distinguished by all measures (individuals—within age—effect). For all measures there is a significant effect due to the difference between the 45 degree tilt and the tilt to standing (position effect). There is, also, a significant effect for all measures due to the difference between sitting after standing and sitting after exercise in the standing position (exercise effect). Moreover, there is a significant time trend in all measures both with (*position* × *time effect*) and without (time effect) respect to differences in position and levels of exercise.

The previous statements concerning the changes after 45 degree tilt, tilt to standing, and exercise are confirmed by the analysis of variance. Differences with age in rates of change are referred to *age* × *time interaction effects*, while differences with age in levels are referred to *age* × *position interaction effects*.

In addition, the sharp systolic blood pressure changes in the 60 year and the 70 year age groups following tilt to standing (tilt position 2) are reflected in a significant *age* × *time interaction* effect within position 2 ($f = 2.62$). The age differences in the time curves for heart rate following the 45 degree tilt are reflected by a significant *age* × *time interaction effect* taken over both positions ($f = 1.75$).

* Figure 1 would seem to disagree with this statement because curves for all age groups are not included.

* Reference is made to table 2, analysis of variance. The statement is referred to age effect and systolic blood pressure both for tilt and for exercise. The F ratios are significant.

TABLE 2.—*Summary of Variance Ratios (F Ratios) for Blood Pressure and Heart Rate Data Following Tilt to 45 degrees and 90 Degrees and Following Sitting after Standing and Sitting after Exercise*

Effect	Code	Error Mean Square	Tilt (to 45° and 90°)					Exercise (before and after)				
			Blood Pressure			Heart Rate	D.F.	Blood Pressure			Heart Rate	D.F.
			Systolic	Diastolic	D.F.[a]			Systolic	Diastolic	D.F.		
Age	A	B	4.90S*	1.96NS	5–134	1.49NS	5–133	6.96S*	2.12NS	5–132	0.20NS	5–132
Individual (within age)	B	H+I+J	176.64S*	227.18S*	134–2278	196.10S*	133–2793	151.76S*	173.84S*	132–2244	158.09S*	132–2793
Position[c]	C	H	43.04S*	167.47S*	1–134	85.24S*	1–133	182.28S*	92.84S*	1–132	116.13S*	1–132
Time	D	I	36.94S*	7.32S*	8–1072	2.33S	10–1330	66.38S*	14.04S*	8–1056	125.73S*	10–1320
Age × Position	E	H	5.05S*	1.25NS	5–134	5.37S*	5–133	7.20S*	1.44NS	5–132	3.61S	5–132
Age × Time	F	I	3.45S*	2.89S*	40–1072	1.75S	50–1330	1.29NS	0.89NS	40–1056	4.23S*	50–1320
Position × Time	G	J	5.99S*	95.57S*	8–1072	11.42S*	10–1330	7.43S*	31.82S*	8–1056	53.94S*	10–1320
Age × Time × Position	K	[b]	0.77NS	28.59S*	40–600	1.26NS	50–640	1.00NS	0.15NS	40–590	8.18S*	50–640
Age × Time (Position 1)	L	I	1.73S	1.01NS	40–1072	1.60NS	50–1330	0.52NS	0.43NS	40–1056	0.69NS	50–1320
Age × Time (Position 2)	M	I	2.62S*	21.60S*	40–1072	0.67NS	50–1330	1.76S	1.30NS	40–1056	6.14S*	50–1320
Individuals × position (within age)	H	—										
Individuals × time (within age)	I	—										
Individuals × time × position (within age)	J	—										

S = Significant ($p < 0.05$)
S* = Significant ($p < 0.001$)
NS = Not significant ($p > 0.05$)

[a] Degrees of Freedom.

[b] Mean square based on variation of initial resting horizontal pre-tilt estimates of appropriate response.

[c] "Position" should read "Exercise" for the second part [Exercise (Before and After)] of this table. Position 1 = before exercise. Position 2 = after exercise.

This latter difference may be attributed to the 45 degree tilt because the *age* × *time interaction* within tilt position 1 ($f = 1.60$) may be significant ($p = <0.10$) while the *age* × *time interaction* within tilt position 2 ($f = 0.67$) is not significant.

To test the conclusion that there was a greater systolic blood pressure drop in older subjects than in young subjects following tilt to 45 degrees, the regression on age of the differences between the systolic blood pressure reading before the 45 degree tilt and the systolic blood pressure reading after the 45 degree tilt was estimated. A t test indicated that the regression was significant ($t_{138} = 19.19$).

Discussion

The instantaneous alterations in blood pressure following change in position (table 1) are compatible with hydrostatic concepts. The heart rate responds very rapidly to compensate these pressure shifts. Statements concerning age differences in volume distribution of blood cannot be made, since they have not been quantitated.

The progressive adjustments of systolic blood pressure following change in position were more or less uniform for all age groups except after the 45 degree tilt where the older subjects showed a larger drop in systolic pressure than did the young. This less adequate response of the older subjects to the small postural shift, may be due to a less sensitive vasomotor response or to a differential aortic distensibility between old and young. On the other hand, the vertical tilt represents a stimulus which effects equal response of systolic pressure in all age groups. This may be the result of the larger, now equally effective stimulus or a differential response between old and young, with structural limitation to the blood shift in the older subject.

Changes in diastolic pressure may be considered to reflect changes in arterial resistance if pulse pressure and heart rate do not change in the same direction. For example, curves of recovery from exercise suggest that despite increased heart rate and systolic pressure during exercise, diastolic pressure was decreased reflecting the vasodilation of exercise. Similarly, the changes in diastolic pressure were opposite to the changes in pulse pressure following tilt to 45 degrees and return to horizontal position. Here the 20 year old group showed the greatest and most rapid change. Following the tilt to standing, diastolic pressure was not maintained as well in the older subjects, although they showed no greater systolic fall than the younger subjects did. These relations suggest that the vasomotor changes normally induced by the postural maneuvers described, were less marked, and less prompt in our older subjects.

Heart rate responses were also more extensive in the younger subjects, although here there seems to be a gradation of response with age instead of a single outstanding age group difference, as in the diastolic blood pressure curves. Heart rates increased sharply in the face of decreased venous return to the heart and decreased sharply with increase in supply (return to horizontal or sitting positions).

Thus, on tilting, the older subjects show slower compensatory responses than do the young.

Systolic blood pressure and heart rate responses to exercise increased with increasing age, while diastolic blood pressure response seemed to be similar for various ages. There was, then, during and after exercise an increase in pulse pressure and heart rate which was greater in the older subjects. These differences might be the result of differences in cardiac output, were it not for the fact that decreased aortic distensibility with age could explain the increased pulse pressure response.

Even without postulating a difference in cardiac output, the fact that the older subjects recover from these greater increases of systolic blood pressure and heart rate more slowly then did the young, plus the fact that the older subjects compensated the changes caused by tilting more slowly than did the young, suggest that there is a component of hemodynamic equilibration at the vasomotor level which may contribute to the slowing of metabolic recovery in older people following exercise. Although the magnitude of this component might be expected to be small, it should

be considered as a possible source of variability in the interpretation of exercise recovery curves.

Summary

Heart rates and brachial auscultatory blood pressures were measured in 140 ambulatory male subjects between 20 and 92 years of age following tilt to 45 degrees, tilt to standing, and step exercise of 222 Kilogram-meters of work in 1.5 minutes.

The data presented indicate that there are age differences in heart rate and blood pressure responses to and recovery from the stimuli employed.

Following tilt to 45 degrees, older subjects showed greater decrease and slower recovery of systolic blood pressure, and smaller increase in heart rate than did the young, while diastolic blood pressure levels remained unchanged in all groups.

Following tilt to standing, older subjects showed a greater decrease and slower recovery of diastolic blood pressure, and smaller increase in heart rate than did the young, while systolic blood pressures decreased similarly in both old and young.

Following exercise of 222 Kilogram-meters (S.D. = 16 Kg.M.) in 1.5 minutes older subjects showed slower recovery from greater increase of systolic blood pressure and heart rate than did the young, while diastolic blood pressures showed similar time curves for different age groups.

The data presented suggest that changes in posture and changes in age should be reflected in cardiovascular and metabolic recovery curves following exercise.

Acknowledgments

The authors gratefully acknowledge the assistance of Nicholas O. Demmey, Charles K. Ferguson, and Fowler White who collected the data, of Dr. Max Halperin who outlined the analysis of variance, and of Mrs. Elizabeth Benser who carried out the computations. For careful criticism of the interpretation of the results, the authors are indebted to Dr. Milton Landowne.

Sumario Español

Inclinaciones y ejercicios normalizados causaron extensos cambios en el pulso y la presión arterial auscultatoria en 140 sujetos hombres ambulatorios entre las edades de 20 a 92 años. Luego de ejercicio similar, los sujetos mayores mostraron un incremento mayor en el número de contracciones cardíacas y en la presión de pulso que el grupo joven, quien compensó los cambios producidos por inclinación más completamente y rapidamente que el grupo mayor. Las respuestas compensatorias de los sujetos mayores se deben considerar en la interpretación del promedio de recobro metabólico luego del ejercicio.

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The Lewis A. Connor Memorial Lecture

The Physiology of the Cardiac Output

By W. F. Hamilton, Ph.D.

THE PRIMARY FUNCTION of the heart is to supply an adequate stream of oxygenated blood to the body. Transportation of other nutrients and wastes is an easy task compared to the transportation of oxygen. Thus, even in the resting state, one fourth of the blood's oxygen is depleted as the blood passes through the body and goes back to the lungs; whereas it picks up only one eighth of its content of carbon dioxide on the same trip. The nutrients and wastes such as blood sugar and urea have an even smaller arteriovenous difference in proportion to blood content.

Thus it would seem that oxygen transport is the strategic function of the circulation and, from that assumption and from many other facts, it can be argued unequivocally that the handicaps resulting from the sudden insufficiency of the circulation in syncope and shock stem directly from failure of oxygen supply. More equivocally, but with some degree of probability, it can be argued that failure of adequate oxygen transport is an essential factor in activating the renal and hormonal mechanisms which cause the kidney to conserve water and salt, and which lead to the edema and plethora of congestive failure of the circulation.[1]

The circulation fails not necessarily because of a weak heart but also because even a normal heart cannot meet the oxygen demand as a result of some maladjustment other than that of the valves or the myocardium. In thyrotoxicosis the oxygen demand is increased; in certain pulmonary diseases and anemia the blood cannot take up its fair load of oxygen[2]; and in certain cases of beriberi there is a subtle physiologic interference with the utilization of oxygen. In all of these conditions there may be failure of oxygen supply and consequent congestive failure while the heart is laboring strongly and doing twice the normal pumping job. For this reason it might be well to think of the syndrome in general as congestive failure of the circulation rather than congestive heart failure.

The circulation rate, or cardiac output, thus does not have simple and uncomplicated relation to the development of heart disease symptoms. In order to unravel the complications of the regulation of the normal circulation and its disturbances in disease it is best to review the methods and their adequacy for measuring the output of the heart.

William Harvey[3] based his argument that the blood did circulate upon the arrangement of the valves of the heart to permit only flow from veins to arteries. As a first instance of the quantitative method in physiology he suggested that the left ventricle contains two or three ounces of blood and, on contracting, ejects all or part of it into the arteries. He was not impelled by the necessities of his thesis to argue for a two to three ounce stroke volume because a single dram per beat would defeat the Galenic tradition and accumulate in the arteries to burst them.

Among the pioneers of the study of the circulation we should also pay our respects to Stephen Hales[4] who made casts of the left ventricular cavity and, assuming that each stroke emptied it, calculated to four figures the cardiac output, the velocity of the blood flow in the aorta and in its branches by dividing the output by the aggregate cross area of the arterial tree at various levels. He located the peripheral resistance—to use modern jargon—in the minute vessels and worked out an explanation for dropsy that needs little extrapolation to seem very modern.

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These earliest workers based their estimates upon anatomic considerations. They could better be called speculations rather than measurements. The first lead to a quantitative measurement that could be applied to a normally functioning animal or man was a brief note by A. Fick[5] who, in 1870, first called attention to the fact that were we to know the oxygen consumption and the arteriovenous oxygen difference as it obtained in the heart, the bloodflow could be readily calculated. History has played a sardonic trick on this estimable and learned gentleman by scattering the dust of obscurity over the monumental treatises to which he gave his life, and attaching his name, in the minds of nearly every medical student, to an evanescent idea that he barely took time to put on paper and to which he never returned.

The subject must have been introduced well ahead of its time because contributions to the field were few and far between for 50 years. The first was an exasperatingly brief note in the Comptes Rendus[6] in 1886 indicating, but not describing adequately, measurements of the cardiac output of dogs. This was followed in 1898 by the classic and meticulous study of the cardiac output of horses by Zuntz and Hagemann.[7] Taking advantage of the fact that the blood of this creature is slow to clot, a catheter was introduced via the jugular vein down to the vicinity of the right auricle. Mixed venous samples were taken during rest, digestion and exercise. The contributions of these workers were of such great merit that Yandell Henderson felt that we should refer to the method of Zuntz and Hagemann rather than the method of Fick.

This was the only study of the cardiac output in the intact animal by direct measurement which attempted to follow physiologic response to changed conditions from 1870, when Fick wrote his famed paragraph, until the 1920's when there was a revival of interest in the control of cardiac output. It was hoped that a key, such as blood pH, would be found to regulate the circulation just as it was thought to regulate the respiration.[8] Search for such a key was naive because the cardiac output seems to be regulated as the summation of the demands for blood by the several organs of the body, each in control, so to speak, of its own blood supply. Much interesting work was done in this period by workers who followed changes in blood flow of animals resulting from drugs,[9] arteriovenous fistulas,[10] hemorrhage, trauma,[11] and pneumonia,[12] to instance a few of the numerous studies.

At the turn of the century no one had the temerity to puncture the human heart or to catheterize its cavities. Credit is due Loewi and von Schrotter[13] for thinking of using the lungs as an aerotonometer to measure the gas tensions of the mixed venous blood and, hence, its gas content. Not only were these authors the first to use the lungs in this manner, but also they were the only ones to use the principle in a nearly impeccable manner. They blocked off a small part of one lung and allowed time for complete equilibrium of the air in that part with the returning venous blood. Others to follow[14, 15] attempted to arrive at equilibrium between the pulmonary air and the venous blood before recirculation and after blocking fresh air away from both lungs.

The results reported by these authors varied between 4 and 8 liters per minute, and it was not clear why they were so erratic. During the twenties and thirties of the present century the computation of the cardiac output from respiratory data became stylized about the procedure of Grollman[15] who promulgated the doctrine that the human circulation time was 25 to 30 seconds (correct figure 10 to 18 seconds) and hence that a respiratory mixture could be left in the lungs for that length of time without exposure to recirculated blood. The figure for cardiac output, had by this method, was 2.2 liters per square meter per minute—about two-thirds the correct figure. It is perhaps fortunate that the procedure overwhelmingly in vogue pin-pointed a figure that was so dramatically in error.[16] Had this not been the case the proponents of respiratory methods would not have given up so easily and the literature would have been stultified with controversy.

It is hardly necessary here, except for completeness' sake, to discuss the brilliant and dramatic story of cardiac catheterization. It

was introduced in 1929 by the intrepid Forssman[17] who, using an ordinary varnish catheter, catheterized his own heart several times. The next year Klein[18] drew mixed venous blood from such a catheter and calculated the cardiac output. Cardiac catheterization was applied during the next decade to the visualization of radiopaque substances injected into the cardiac cavities. Another significant advance was made in that a nonwettable plastic catheter was developed that minimized the danger of intravascular clotting. The time was ripe in 1941 for Cournand and his co-workers to open up a new book[19]: the study of the cardiac output in man, the unraveling of the pressure and flow relationships in the cardiac chambers and the great vessels of the pulmonary and systemic circulations. With the work of groups led by Stead, Bing, Dexter, McMichael and others, as well as with the continued work of the Bellevue group working with Cournand, the pages of the new book have been filled with accounts of circulatory dynamics in normal man, in shock, in congenital heart disease, under the influence of drugs and in cardiac and pulmonary failure.[1, 2, 20-26]

Attention has recently been called[27] to a source of error which is inherent in the Fick procedure—and in all other "dilution" procedures—when the subject is not in an absolutely steady state. It is easily imaginable that cyclic changes in a heart with a congenital anomaly or sudden vasomotor changes would result in a change in the oxygen content of a venous sample so that the arteriovenous difference would change from 40 to 80 cc. per liter. The sample might be a mixture of the two bloods in equal proportion and would indicate an average arteriovenous difference of 60 cc. per liter. Assuming an oxygen consumption of 240 cc. per minute this average arteriovenous difference would correspond to a bloodflow of 4 liters per minute. This conclusion is based on the false implied assumption that the flows, when the arteriovenous difference was high and when it was low, can be taken as equal to each other and hence averaged together. As a matter of fact the flow during one period was at the rate of 6 liters per minute and, during the other period, at the rate of 3 liters per minute, and the volume average, as distinguished from the time average, is 4.5 liters per minute instead of 4.

This error in the Fick calculation tends to be minimized by two things. First, the time average tends to follow the direction of change in the volume average, clinging more closely than it should to the lower of the two figures. Second, any mixing of blood in the cardiac, venous, or arterial stream would tend to make the sample a true volume average. Thus, in calculating the pulmonary bloodflow in case of a shunt from left to right, cyclic changes in oxygen concentration of blood would be less in pulmonary artery samples if the shunt were in the auricle than if it were in the ventricle, and less in this case than if a patent ductus were involved.

Since this source of error is involved in all dilution methods, it cannot be used to explain the fact that one dilution method gives an upward trend and another a downward trend.[28] To evaluate this error in practical terms it is necessary to compare results with a volumetric method. This has been done and the two agree under the limited conditions tested.[29, 30]

Another and more serious source of error results from the storage in, or liberation of, gas from the body, including the lungs. A case of congenital heart disease with cyanotic episodes has been described[31] in which lowering of the systemic resistance caused a cessation of lung blood flow and of oxygen uptake. The patient lived during this episode on her blood oxygen and by means of anaerobic metabolism. By the Fick calculation she would have no cardiac output and yet her heart was pumping strongly. As the organism goes into or comes out of an anoxic state the Fick calculation is dubiously related to the cardiac output.

The vagaries of cardiac output calculations from carbon dioxide production and venous-arterial carbon dioxide difference are such that the measurement is commonly ignored. The unreliability of the Fick method when carbon dioxide is used may be related to the fact that small changes in ventilation strongly influence carbon dioxide storage by the body and a steady state is hard to reach.

In order to trace the growth of our subject in a logical fashion it is best to give an account of another method for measuring the cardiac output and cognate quantities. I refer to the injection method which, like the Fick method, is a dilution procedure. It was introduced into the literature by Stewart in 1897,[32] and has been used by various authors since.[33, 34, 35]

The substance by whose dilution the blood-flow is gaged is injected into the blood stream instead of being added to it or taken from it by physiologic process. An example will illustrate. Twelve milligrams of a substance such as a blood-volume dye, which remains in the vascular system, is injected into a vein. A series of samples is taken from an artery whose dye concentration—after the lapse of a few seconds—begins to increase, to reach a peak and then to descend exponentially[36] until it rises again as a result of recirculation. From the nature of the exponential fall of concentration it is simple to plot the time concentration curve of dye on its first circulation. If the dye concentration curve persists over a period of 30 seconds and its average height is 4 mg. per liter, the 12 mg. injected has been diluted by 3 liters of blood in 30 seconds or by a cardiac output of 6 liters per minute (fig. 1).

This method has been checked against measured flow in models,[37] and against the Fick method both in dog[38] and in man (fig. 2).[39, 40, 41] Its errors in measuring the cardiac output are probably no greater than those of the Fick method and, in addition, the volume of blood in the heart, lungs, and great vessels (from the point of injection to the point of sampling) can be calculated from the dye concentration curve by multiplying the mean circulation time by the flow (fig. 1).[36]

The accuracy of this volume calculation has also been checked by numerous experiments in models.[37] There are large variations in the central volume which can be produced experimentally[42] and are seen in disease.[35] Our earlier idea was that the most distensible part of this vascular bed was that of the lungs. On this basis it was assumed that the huge increase in central volume seen in congestive failure, or after large doses of epinephrine in dogs, was the result of pulmonary congestion.

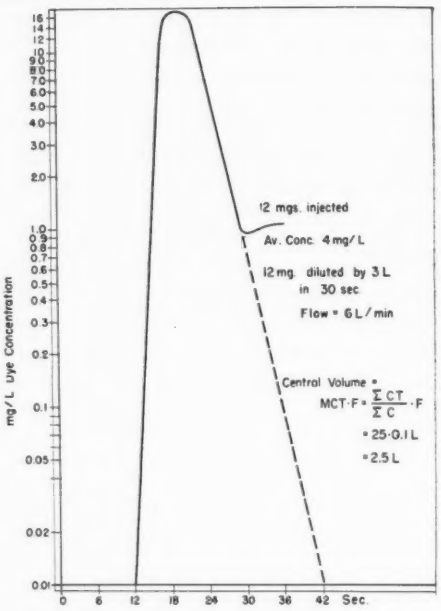

FIG. 1. Concentration curve resulting from the injection of dye into a vein at zero seconds. From this experiment the flow, the total circulation time, the mean circulation time, and the volume of blood in the heart, lungs, and great vessels can be measured.[36]

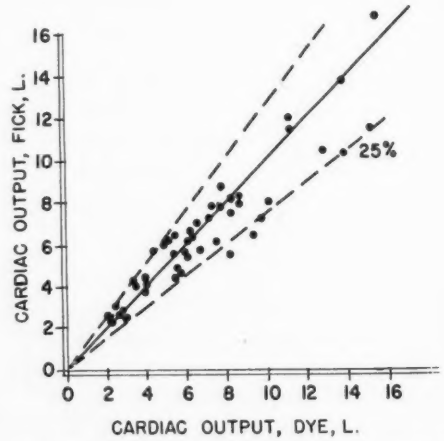

FIG. 2. Plot of simultaneous measurement of the cardiac output in liters per minute by the direct Fick method and by the dye injection method.[38]

Recent quantitative x-ray measurements[43] have made it seem that enlargement of the heart by very large increases in residual blood will

account for all, or nearly all, of the changes in the central volume. Indeed, the heart of a dog who has received an overwhelming dose of epinephrine will contain 13 cc. per kilogram of body weight or 37 per cent of its lethal bleeding volume. The fact that increased pulmonary intravascular pressure does not necessarily result in increased pulmonary blood volume is borne out by measurements on man.[44, 45]

An unfortunate misconception has gotten into the literature[44] relative to the calculation of the mean circulation time. Ebert and his collaborators would have it that the planimetrically measured median circulation time can be used to calculate the capacity of the stream bed. This is true only if the dye concentration curve is symmetric. In a series of dye curves from dogs, use of the median circulation time to calculate central volume was in error by 50 per cent.* The mean circulation time, or the average time it takes all the dye to pass is computed as the center of gravity of the curve or:

$$MCT = \frac{\Sigma\, CT}{\Sigma\, C}$$

Details of the calculation are shown in the paper referred to in reference 36.

If the central blood volume or some definite part of it were simultaneously and homogeneously mixed with the injected substance, one could calculate the magnitude of this volume from the slope of the downstroke or washout of the dye concentration curve.[44] We have never felt that the initial assumption was satisfied in the animal and have shown that in ordinary conditions of flow in models the volume which determines the slope is rather remotely related to the total volume.[36] We therefore have little faith in the calculation of physiologic volumes from the washout slopes of dye concentration curves.

This is even more to be emphasized by the fact that pulmonary flow is in all probability entirely different from flow through a chamber

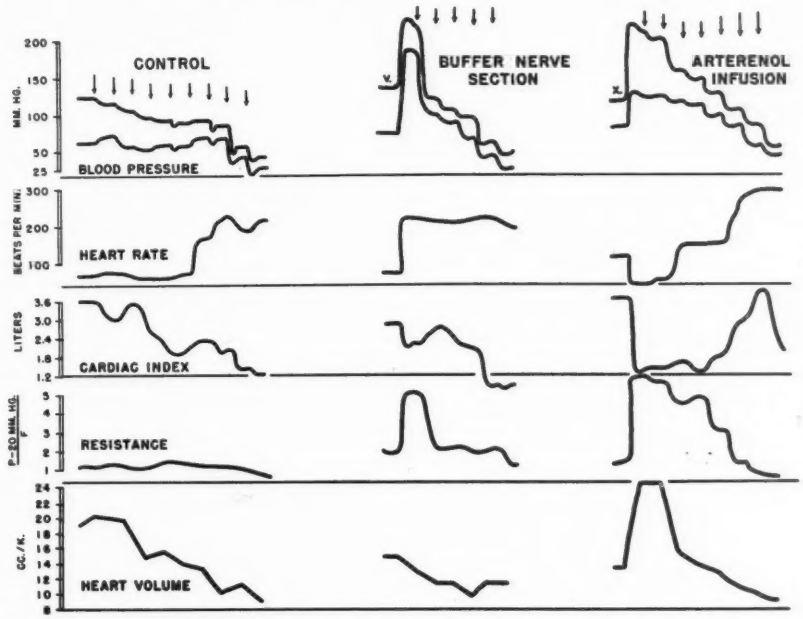

FIG. 3. Changes in circulatory factors when dogs under different conditions are bled in steps of 5 cc. per kilogram.[43]

* Dow, P. Personal communication.

where dye and blood are completely or even incompletely mixed. In the perfused lungs there is a long wait after injection for the dye to appear; in the mixing chamber it appears instantly. Moreover tubular flow does not give a simple exponential washout type of curve[45] and the curve from lung perfusion experiments resembles that from tubular flow rather than that from chamber washout (unpublished work). The exponential washout curve obtains, however, when heart and lungs are perfused in series.

The laborious measurement of dye concentration in many samples has contributed a technical hazard that has served to make the method relatively unpopular. There are in process of development several procedures for measuring the concentration curve of dye in the arterial stream by means of a photoelectric cell and a recording galvanometer. The blood is put in front of the photoelectric cell either in a heated ear pinna or in a translucent tube connected to the artery by a puncture needle.[47, 48, 49] The dye concentration read from a curve made in this manner is hard to quantitate, but the method promises to be a very useful one. A similar labor saving approach is to attach a radioactive atom to an injectable substance which remains intravascular.[50]

Besides the dilution methods for measuring the circulation rate we have methods in which the aortic stream may be metered volumetrically by the cardiometer,[51] rotameter,[25, 30] or electromagnetically.[52] To use these methods it has been necessary to open the thorax and to make the measurements of an abnormal circulation. Nevertheless, a great many important advances have been made by these methods.

The methods considered so far are best called primary methods in that, if reasonable assumptions are granted, they are direct measures of the cardiac output. Contrasted to these are methods which are best referred to as empiric methods, methods which achieve their validity from constants derived by comparison with a primary method. Among these are ballistocardiography,[53] x-ray kymography,[54] electrokymography,[55] and the calculation of the cardiac output from the pulse pressure curve. Time will permit the discussion only of the last of these methods.

Evaluation of the stroke volume from the pressure pulse was first suggested by Erlanger and Hooker.[56] Quantitative adjustments were made against the ethyl iodide method in a few subjects by Bazett and his co-workers[57] and against the nitrous oxide method by Liljestrand and Zander.[58] A few years ago careful measurements were made of the volume and distensibility of 48 human aortas taken from many age groups and from patients with various diseases (fig. 4).[59] These aortas showed twofold variation in actual volume which could not be predicted from age or history. On the other hand, the increase in volume with increased pressure was much more constant from group to group and individual to individual. Since pulse wave velocity changes with distensibility relative to the size of the aorta rather than the more constant distensibility in actual volume, it was thought best

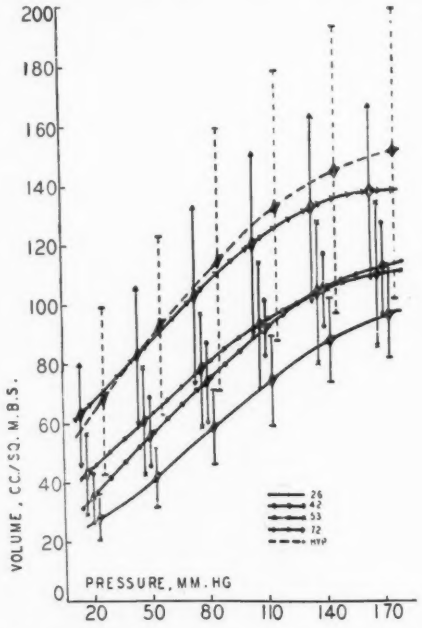

FIG. 4. Relation of the volume of human aortas of different age groups to pressure. Vertical bars are standard deviation.[59]

o avoid the complications of a pulse wave elocity correction, such as used by Bazett[57] nd by Broemser[60] and others, and simply elate pulse pressure to stroke volume. This as done for a series of patients from the di- ect Fick measurements made in Cournand's aboratory and a smaller series from the eorgia laboratory (fig. 5).[59] By a strange oincidence it was found that the best fit was iven when 1 cc. of stroke index was made quivalent to 1 mm. Hg of pulse pressure. hus if the arterial pressure is 120/80 the verage stroke index would be predicted to be 0 cc. These values hold only at ordinary pres-

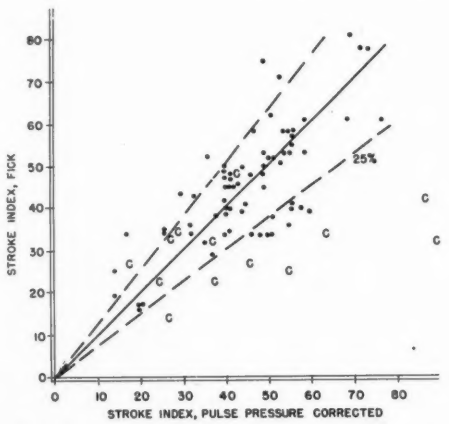

FIG. 5. Relation between stroke index as calculated from the corrected pulse pressure and as determined by the direct Fick method.[59] *C* = cases of congestive failure.

sure levels. The prediction of the stroke volume is of about the same order of accuracy as that made by the ballistocardiograph. It could no doubt be made more accurate if, at the beginning of an experimental procedure, an actual output measurement (for example, dye curve) were made to "calibrate" the distensibility of the subject's arteries.[61] After such a calibration the stroke volume could be followed from beat to beat during an experimental procedure.

Since dogs die young and their arteries rarely show the effects of aging and disease, a potent cause for the random variation in the relation between stroke volume and pulse pressure is not seen in these creatures. Careful measurement has shown that all aortas of dead dogs are very much alike as to their size in relation to the size of the body and as to their distensibility.[62]

This fact justified the attempt to measure in detail the amount of blood required to expand the arterial tree as the pulse wave passes out over the arteries (fig. 6).[63] This is necessary because the contour of the pulse wave differs very greatly in various experimental conditions. In some cases the pressure at the moment of aortic valve closure is very high and the aortic arch greatly expanded. In other cases the pressure in the arch has gone back to the diastolic level when the valves close; and the pulse volume is stored in the aorta and its branches farther down.

These considerations caused us to measure the distensibility of the four main subdivisions of the arterial tree (arch, head, viscera, legs) and find what part of the pulse wave has arrived at each of the subdivisions at the time the aortic valve has closed. This gives us the effective pulse pressure in each part of the arterial tree. Knowing the distensibility of these parts and the effective pressure change brought about by the pulse wave, the total uptake of the aorta and its branches (corrected for body size) could be summated.

The arterial uptake is only a part, but a significant part, of the stroke volume (stroke index). In addition, there is the blood which drains out through the arterioles during systole. Arteriolar outflow follows quite closely the law of Poiseuille, that is, it is the product of pressure and time if the arterioles remain the same. Since the uptake is known and must drain out the arterioles during diastole, it is possible to calculate the arteriolar drainage in cubic centimeters per millisecond per millimeter of mercury from the diastolic part of the curve and apply it to the systolic part of the curve. This systolic drainage plus the uptake is the stroke volume (stroke index).

This formidable calculation has been stylized by means of tables and graphs so that it may be accomplished in 15 minutes or so. When dogs are under the influence of drugs, hemorrhage, neurogenic or renal hypertension, or

traumatic shock, the pulse pressure method gives results which compare closely with those of the Fick procedure or the dye injection method (fig. 7). This has been confirmed by the Baylor group (fig. 8).[64, 65] It was checked against the rotameter in dogs by Longino and Gregg and found to give rather close agreement when the rotameter was placed in the pulmonary artery (fig. 9).[66]

When, however, the rotameter is placed in the right auricle and vena cava the pulse contour calculations become too large. The arterial uptake under this and other severe conditions is much less than it is normally with the same pulse pressure. The aorta has suddenly become less distensible, has gone into rigor. Unfortunately no change in pulse wave velocity indicates the change in aortic rigidity.[62, 67]

It has been rather a disappointment to find that the pulse contour method will not calculate the cardiac output under all conditions,[67, 68] even though it will under most conditions.[69] Every bafflement is a stimulus to further work and, I hope, greater insight will result. Why is it that the arteries lose their distensibility, go into rigor? Is it a reversible phenomenon? What is its fundamental cause? Why is the change always a decrease, never an increase, in distensibility? I hope that these questions will be answered before long.

After having spent so much time evaluating the methods of measuring the cardiac output we are justified in raising questions relative to

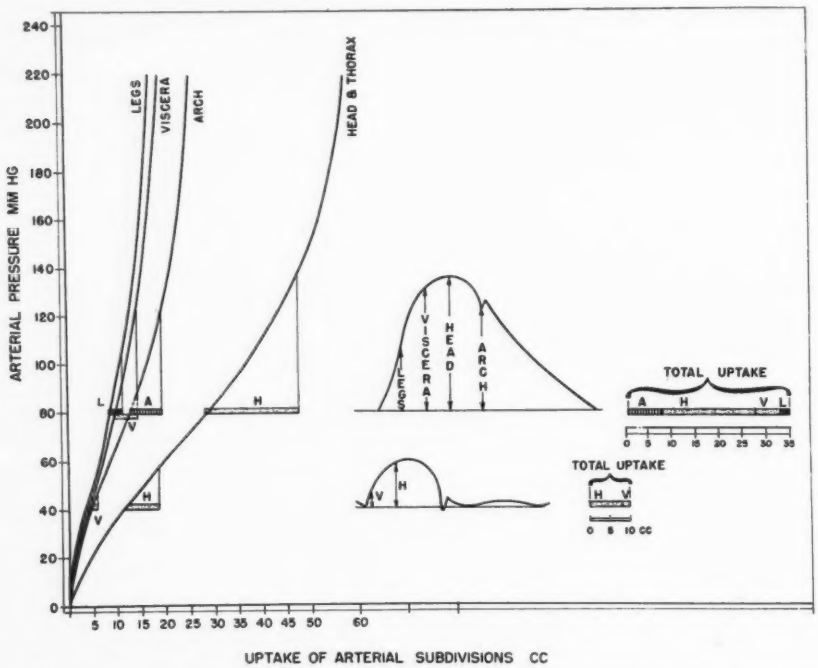

FIG. 6. Diagram of two pulse curves and of the distensibility of four divisions of the arterial tree. The vertical lines referred to the ordinate scale indicate the pulse pressure in millimeters of mercury distending the different parts of the arterial tree at the time of aortic valve closure. These pulse pressures are laid off on the proper distensibility curve and the uptake of the parts summated to make the total uptake as read on the lower scale in cubic centimeters per square meter body surface. The upper pulse wave, with its greater pulse wave velocity, distends all four arterial divisions. The lower pulse curve, with its shorter duration and slower pulse wave transmission, distends only two parts when the valve closes. For calculation of stroke index from uptake see text.[63, 67, 68, 69]

ar insight into fundamental mechanisms by means of which the cardiac output is regulated. That there is such regulation, that it is adaptive and serves the ends of the organism is beyond

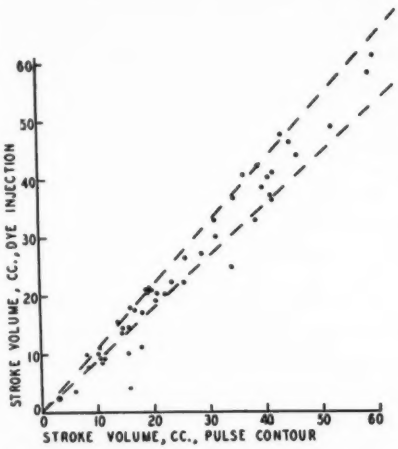

FIG. 7. Relation of stroke volume as measured by direct Fick method or dye injection method to a simultaneous calculation from the pulse contour. Intact dogs under various experimental conditions including shock, hemorrhage, hypertension, and drug action.[63]

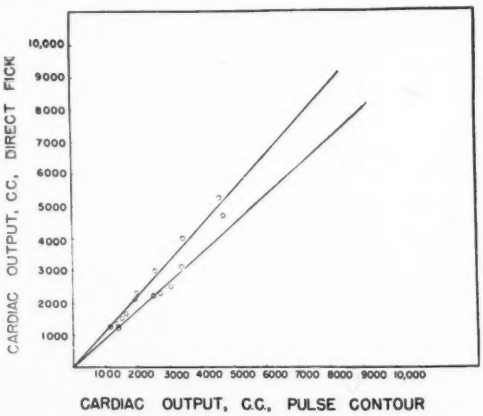

FIG. 8. Relation of measurements of stroke volume by Fick and pulse contour method (Huggins and associates[64]).

dispute. The cardiac output can change from a resting figure of 6 liters per minute to a value of 15 in mild exercise,[70, 71] and probably much more with heavy exercise. The increase is brought about by an increase in stroke volume as well as by an increase in rate. The increase in stroke volume is minor, as was long held by Y. Henderson.[51] Under conditions of circulatory handicap, such as hemorrhage, the cardiac output may be reduced to half the resting figure or even less. Thus the circulation rate may be varied sixfold or more but regulation is such that the driving force, that is, the mean blood pressure, varies comparatively little (10 to 50 per cent).

The fact that there is a relatively constant blood pressure in the face of large changes in flow implies a regulation of the cardiac output to match the peripheral resistance or vice versa. It can be shown, I think, that the circulation rate is governed primarily by the peripheral resistance and that the output of

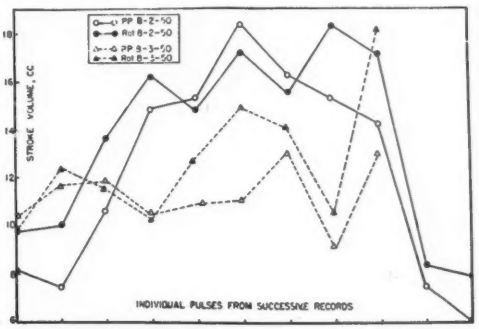

FIG. 9. Consecutive comparison of rotameter and pulse contour measurements of stroke volume (Longino and Gregg[66]).

the heart is secondarily regulated so as to maintain a relatively constant arterial pressure.

The peripheral demand for blood expresses two needs: the need for oxygen by active tissues and the need to dissipate heat. Both of these demands are satisfied by local dilation, under local or specific control. When muscles, glands or viscera become active their arterioles dilate and their blood supply increases. This is mainly in response to local chemical influences and is dependent, to little or no degree, upon reflex adjustment of vascular tone. When we become overheated, hypothalamic reflexes are activated which cause cutaneous dilation and heat is dissipated. Both of these vasodilator mechanisms are prepotent, that is will hold

vessels open in spite of vasoconstrictor outflow from the medulla.

The effect of these local dilations, mediated by mechanisms which have no relation to the control of the heart beat, is to lower the peripheral resistance and, hence, the arterial pressure, and to set in action reflexes originating in the aortic arch and carotid sinus which accelerate the heart and restore the arterial pressure, but with an increased output. Peripheral constrictor mechanisms such as cold, abatement of activity, and vasoconstrictor drugs bring about the opposite response by the peripheral resistance and, hence, secondarily by the heart. The pressure rises but is reflexly restored toward normal by cardiac slowing and a reduced cardiac output.

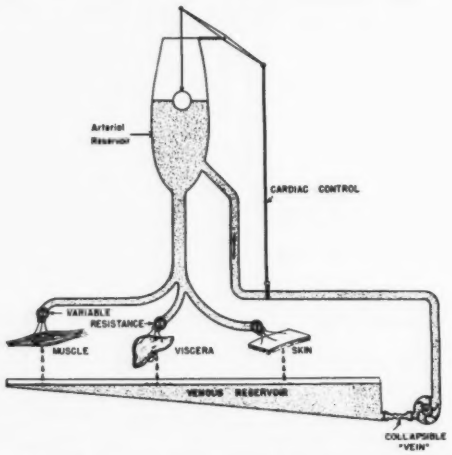

FIG. 10. Schema to illustrate the theory that the primary control of the output of the cardiac pump rests in the variable resistance controlled at the level of the peripheral organs and that cardiac regulation is secondary to pressure changes in the arterial reservoir.

It must be recognized that these relationships are often hidden by other things going on at the same time. Thus in exercise the peripheral resistance is half that in rest; in a study of the effects of exercise the arterial pressure increased 50 per cent, and the cardiac output more than doubled while the oxygen consumption increased about sixfold.[71] The fact that the heart rate doubled cannot be due to a lowered peripheral resistance because the arterial pressure has just increased. Nervous and hormonal stimulation of the heart, arising directly from the excitement of the effort, seem to have played a prepotent role over the reflex slowing which usually accompanies a rise in pressure.

Moreover, the nervous tensions of anxiety and other emotional states alter the peripheral resistance, and this alteration, acting through the secretion of epinephrine and the direct action of the sympathetic system, is different in different species. Thus, in man, anxiety and emotional disturbances dilate blood vessels in the muscles and reduce the peripheral resistance as does the injection of epinephrine.[72-76] On the other hand it is difficult to demonstrate a primary reduction of resistance upon the injection of epinephrine into dogs.

In addition to this psychogenic anticipatory pressor pattern there is another response which, acting at the same time, tends further to complicate the simple relation between increase or decrease in peripheral demand and increase or decrease in cardiac pumping. This is the pattern of arterial pressure regulation through changes in the peripheral resistance as well as through changes in cardiac pumping. Thus the arterial stretch receptors are connected reflexly to produce vasoconstriction when the arterial pressure is low and to produce vasodilation when the arterial pressure is high. If there should be a local demand for blood (oxygen) at the same time that general blood pressure regulation demands vasoconstriction, there is a contest for prepotence between the two tendencies. This contest is decided beforehand by the vasculature of the brain and heart. These blood vessels cannot constrict so as to deprive the vital organs of a steady oxygen supply as can the blood vessels of the leg and to a lesser extent those of the viscera. Even in the vascular beds that are best able to constrict we can well think of a constant conflict between the effect of anoxic chemical changes producing vasodilation (provided the arterial pressure is high enough to prevent the elastic closure of minute blood vessels) and the tendency for constriction under central blood pressure regulation.

The conflict between the effects of local

demand and of general regulation can be illustrated by the following. When one lies recumbent, gravity returns blood to the heart more easily, filling it better, and mechanically increasing its pumping action. At once the heart is reflexly slowed and vasoconstrictor tone is lessened because more impulses are being generated by the arterial stretch receptors in response to a small and aborted rise in arterial pressure. This pattern of response results in a lowered peripheral resistance and an increased cardiac output in spite of the fact that the metabolic demand for blood is lessened.

Conversely the results of trauma or hemorrhage handicap the venous return and lessen the pumping action of the heart. In response to lowered arterial pressure the heart accelerates and the arterioles constrict. This happens in spite of the fact that a very low venous oxygen tension indicates that the tissues are greatly in need of oxygen. This response may not be in the best interests of survival, as witnessed by the fact that when the vasoconstrictor response is aborted by Dibenamine the animal endures the hypotension of shock better than without the drug.[77, 78]

Not only do adjuvant mechanisms complicate responses but the responses themselves are of extraordinary accuracy and delicacy. On injecting a small dose of epinephrine, or other constrictor drug, the heart often appears to slow before there is any visible rise in pressure. In interpreting this it has been suggested that the reflex slowing is teleologic and anticipatory. To quote a statement which has become "classic" in our discussions around the laboratory, "The decreased cardiac output . . . is attributed to reflex adjustments initiated by the threatened (sic.) increase in blood pressure which would result from constriction of cutaneous vessels."[79] In contrast to this we may assume that the reflex slowing has a very delicate threshold and that the response is due to a rise in pressure that escapes notice—is in reality the same stimulus that seems logically to produce the slowing, a few seconds later, when the pressure rise is appreciable.

This principle of accurate physiologic adjustment is illustrated in the control of bloodflow through the Goldblatt kidney. The clamp, when it is first applied to the renal artery, must in the nature of things reduce the bloodflow to the kidney. Soon, by hormonal mechanisms, the blood pressure rises and, when a steady state is reached, the renal bloodflow is back within normal limits. Is it not reasonable to believe that physiologic compensations are accurate and delicate enough to bring the renal bloodflow back to a figure that, to our crude measures, seems normal? What other compensatory function would the hypertension have?

Thus we might assume as a working hypothesis, that whatever variable is held most constant is the key to natural physiologic regulation. The wisdom of the body is such that *by the time a steady state is reached*, under new demands, the important variable, the one with survival value, is regulated within physiologic limits. Thus in looking at the regulation of respiration we would hunt, not for something that is abnormal when the respiration is increased or decreased, but rather for something which has been returned to normal by the changed respiration. The answer on this hypothesis of accurate regulation would be the hydrogen ion concentration of the blood for respiration, kidney blood flow for renal hypertension, and arterial pressure for the regulation of the circulation.

FIG. 11. The effect of a small dose of epinephrine in producing a slowing of the heart before any conspicuous increase in pressure has occurred.

In discussing the control of cardiac output, the classic experiments of Starling and his collaborators must be taken prominently into account.[80, 81] Starling's experiments were made on the heart-lung preparation, a preparation in which the heart could respond only by means

of its intrinsic myocardial mechanism. His evidence showed conclusively that when the heart is deprived of the natural reflex mechanisms, when its rate is held constant and hormonal stimuli are not acting, an increase in the aortic pressure or in the venous return brings about an increase in diastolic cardiac size. He showed moreover that within physiologic limits, this increase in diastolic size was self limiting because it also brought about an increase in the effectiveness of cardiac pumping and an increase in oxygen consumption by the heart.

that are of theoretic importance in relation to the diastolic size of the heart and Starling's law. In exploring in the normal animal such aspects of cardiac action as stroke volume, cardiac work, systolic and diastolic pressure, and heart rate, it was found that only heart rate clearly and uniquely correlated with diastolic size as computed from x-ray silhouettes.[43, 82] When the heart accelerates—pumps more blood—it becomes smaller and when it slows it fills more and becomes larger. Changes in rate then work against any application of the Starling law in the intact animal.

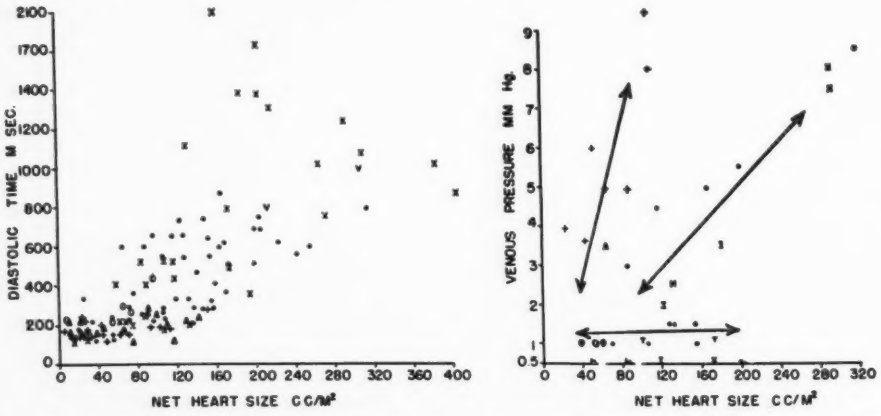

FIG. 12. *Left:* The relation of cardiac blood volume to filling time. The various symbols indicate experimental procedures such as buffer nerve section, epinephrine infusion, vagus stimulation, and others. These procedures do not indicate significantly different trends or slopes.[82]

Right: Relation of net heart size to venous pressure. The group indicated by the lower arrow are slowly beating hearts which become large with low venous pressure; those indicated by the upper arrow are rapidly beating hearts that remain small in spite of high venous pressures.[82]

It is not the purpose of the following paragraphs to cast doubt upon the fundamental truth of the insight into cardiodynamics which is embodied in "Starling's Law of the Heart," but rather to inquire into the manner in which the reflex adjustments available to the intact animal enable him to safeguard his heart from stresses which illustrate Starling's law.

In making adjustments to changes in flow and in aortic pressure the most obvious physiologic change is in heart rate. It has been known for more than a century. It is in response to pressure changes in the aorta and carotid sinus, and brings about changes in heart size

These same physiologic reflexes which control the rate of the heart also control its strength of beat. Sympathetic stimuli which accelerate the heart augment its strength of beat and make it empty more completely and become smaller. Under sympathetic stimulation, then, the heart is smaller, not only because it is faster, but also because it is stronger.

An opposite effect results from parasympathetic stimulation. Vagus beats in man,[82] if not in the dog, are weaker than normal beats and the heart under parasympathetic influence is larger, not only because it is slower and fills more, but also because it is weaker and empties

ess. Changes due to sympathetic and parasympathetic stimulation thus guard the heart against the stresses implied in the application of Starling's law.

Caution must be urged against gaging diastolic heart size from the venous pressure. In the first place there are two venous pressures, right and left, and if we are to measure heart size at all we must measure that of the two hearts together. In the second place when the heart rate is rapid the venous pressure may rise to great heights and the heart still remain small.[81] It seems that the process of myocardial relaxation prevents cardiac filling unless there is plenty of diastolic time for the relaxation to take place. Thus large, slow hearts are seen with low venous pressure, and rapid, small hearts are seen with high venous pressure (fig. 12).

The myocardium is a contractile engine whose elastic properties enable it to do work against pressure. The amount of work which it does and, more importantly, the amount of blood which it ejects is dependent upon the pressure against which it works. Thus if the aorta is pressed shut the stroke volume and often the work per beat diminish with the next beat and before any reflex adjustments can have taken place. Similarly there is an immediate increase in stroke volume and often in work per beat when the occlusion is released.[84] The same immediate mechanical control of the stroke volume obtains when an arteriovenous fistula or surgical arteriovenous shunt is occluded or opened,[84, 85, 86] or when a massive vascular area is shut off until, through the process of reactive hyperemia, there is local vasodilation.[86] Release of such occlusion results in an immediate increase in stroke volume even though cardiodynamics are not much changed by the occlusion itself.

The fact that the stroke volume will change twofold or more under these conditions necessitates the belief that there is a residual volume of blood in the heart ready for instant mobilization, and further reserve waiting in the venous reservoir. As the aortic pressure is lessened, the residual blood is evacuated, the heart becomes smaller, the stroke volume larger and the work increased. These changes all occur in reverse when the aortic pressure rises. These mechanisms, even though they are intrinsically myocardial in nature, also militate against a clear application of the Starling law.

It seems from the considerations above that the reflex influences to which the normal heart in the intact animal is subject cause the heart to accelerate and hence to decrease in diastolic size when there is a peripheral demand for an increased bloodflow, and to increase in size when the peripheral demand is lessened. Thus

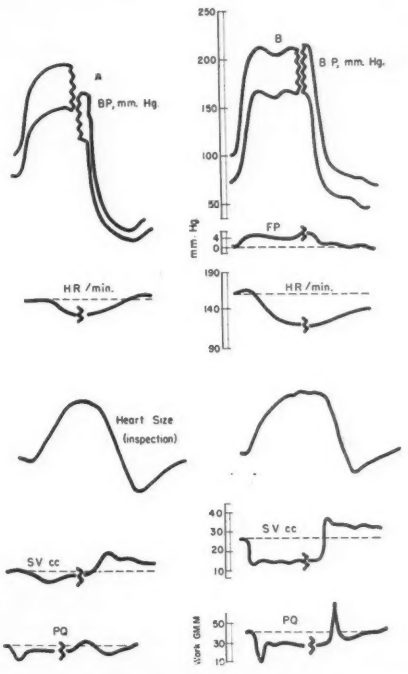

FIG. 13. Circulatory changes resulting from occlusion and release of the aorta. [4]

the normal heart is protected against, and does not react to, the stresses imposed upon it in Starling's experiments.[80, 81]

What then is the role of Starling's law? We can say, as some have, that it operates when, consequent upon respiratory fluctuations in venous return and resulting fluctuations in filling pressure, there are parallel fluctuations in stroke volume.[87] While this is technically an example of Starling's law the situation does not fulfill the implications of his

thesis. To my mind Starling's thesis is that the increased force of contraction and metabolism consequent upon myocardial stretching can enable the heart to overcome a real stress.

It was well known in Starling's time that sympathetic influences, hormonal and reflex, increase the heart beat and that parasympathetic influences decrease it. By means of his heart-lung preparation he ruled out these influences and held everything constant except increased diastolic size and its cardiodynamic consequences. When heart size, and heart size alone, was varied the conclusion was inescapable that the strength of the contraction varied accordingly. It increased as heart size increased up to a certain limit and then fell off.

In cases of heart disease the reflex reserves have been exhausted. The sympathetic influences which tend to keep the heart small have worked at their maximum but have not sufficed. The heart has fallen back upon the Starling mechanism and, by increased diastolic size, has compensated the weakness, or has been overloaded and given out.

The evolution of the intricate adjustments outlined in so cursory a fashion is very puzzling. It seems best to regard them as having been developed as responses to a stress or emergency that can be answered by muscular effort. Thus the need for conservation of water that leads to the oliguria of exercise leads also, in the continued and desperate effort to maintain life under the handicap of heart disease, to the inundation of the tissues in cardiac dropsy. Similarly the hyperpnea of exercise leads to the dyspnea of heart disease, and the excitation of the sympathetic system in exercise is linked with generalized vasoconstriction of traumatic shock.

These responses have evolved as useful stratagems in their original setting as emergency mechanisms, but they have no survival value as compensation for chronic degenerative conditions. This results from the fact that nature is indifferent to the survival value of things that develop after reproductive life is over. Neither an adaptation nor a handicap is relevant to the process of evolution if it develops late in life. For this reason vicious cycles are often the aftermath of degenerative disease. Thus it is customary for the physician to allay the dyspnea of heart disease with a sedative, though its analog, the hyperpnea of exercise, is regarded as a useful response. The dyspnea of heart disease is a vicious cycle and the welfare of the patient demands that it be aborted. Similarly we abort the oliguria of heart disease with diuretics but not the oliguria of exercise. The former is a vicious cycle, a response that has not been culled from the stream of inheritance by the rigorous process of evolution.

It may well be that, as medicine turns more and more toward geriatrics, vicious cycles resulting from late degenerative disease will confront the physician more often. It will be truly a test of the intelligence of the physician and his fundamental background for him to tell the vicious cycle from the useful response, for him to learn to interfere with the one and help the other.

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Failure to Reduce the Size of Experimentally Produced Myocardial Infarcts by Cortisone Treatment

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Cortisone, whether used prophylactically or therapeutically, did not appear to have any beneficial effect in reducing the size of the myocardial infarcts produced by coronary artery ligation in dogs. No significant differences were noted between the control and cortisone-treated animals in respect to the vascularity of the infarcted area or the rate of healing.

JOHNSON, Scheinberg, Gerisch and Saltzstein reported recently that cortisone reduces the area of residual fibrosis resulting from experimental acute coronary occlusion.[1] Since the need for a method of reducing the size of myocardial infarcts is well recognized this report received much attention even prior to publication in this journal. Unfortunately, the result of similar experiments to be detailed here fail to confirm the claims made by Johnson and co-workers.

Procedure

Two series of experiments were performed. In the first series 8 of 15 dogs were treated daily with 10 mg. per kilogram of cortisone acetate subcutaneously, starting six days prior to ligation of the left anterior ramus descendens coronary artery. The remaining seven dogs were operated upon but received no cortisone treatment. The coronary arteries were ligated via a conservative intercostal approach by the two-stage technic of Harris[2] at sites varying from 10 to 33 mm. from the point of origin of the artery. The cortisone injections were continued throughout the experiment, and each experiment terminated at the time indicated in table 1. Observations were made relative to the nature and amount of pleural and pericardial adhesions, the external appearance of the hearts, and the size of the infarcts as revealed by serial sectioning of the fresh specimens. Sections were taken for microscopic examination after suitable fixation in formalin.

After learning that our cortisone dosage was much higher than that used by the Detroit group[3] a second series of experiments was undertaken which followed their design except where more physiologic procedures seemed desirable. Fourteen dogs were subjected to standardized ligation of the ramus descendens artery. The arteries were ligated by the two-stage technic at the point where the posterior margin of the left atrial appendage overlies the vessel. This corresponds roughly to the "high ligation" described by Johnson and associates.[1] Seven dogs received an intramuscular injection of .3 mg. per kilogram of cortisone acetate at the precise moment of complete occlusion of the artery and daily thereafter for the duration of the experiment. The remaining seven dogs were untreated. All dogs in this series received 200,000 units of penicillin daily for the first four postoperative days. Each experiment was terminated two weeks after coronary occlusion, the thorax carefully opened and the contents thoroughly examined before excision and fixation of the heart in formalin. After thorough fixation the site and completeness of ligation were verified on each heart before preparing 0.5 cm. serial sections. The outline of the infarct revealed on each section was traced on a glass slide, the trace transferred to tracing paper and the area of each trace determined by planimetry. The volume of each infarct was calculated by applying the formula for the calculation of the volume of a cylinder. Sections were then taken for microscopic examination.

Results

First Series. Considerable variation was noted in the size of the infarcts in the control series (table 1). The size of the infarct did not correlate well with the site of occlusion. This observation confirms the experience of others.[4] On comparing the size of the infarcts in the control series with the size of those in the cortisone series it is evident that by this method of measurement the infarcts are not smaller in the cortisone-treated hearts. As a matter of

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fact, the largest infarct (dog 14) occurred in a cortisone-treated animal, while the smallest (dog 3) occurred in a control animal.

Postoperative infections were more numerous in the cortisone series because antibiotics were not used prophylactically. However, the size of an infarct is determined within a few minutes after occluding the artery.[5] Postoperative infections, therefore, could influence the rate of healing, but not the size of the infarct.

where between two and four weeks after the infarction (table 2). Well-healed infarcts were seen as early as three weeks after the infarction. The only possibly significant difference between the control and cortisone-treated dogs might be the persistence of large necrotic areas in dog 13 (four weeks) and dog 15 (nine weeks), both cortisone treated. Both of these dogs had rather severe wound infections at the termination of the experiment. It may be noted that

TABLE 1.—*Observations on Gross Examination of Hearts from Control and Cortisone-Treated Dogs*
First Series

Dog No.	Post-operative time	Site of occlusion	Size of infarct	Comment
			Controls	
	weeks	*mm.**	*cm.†*	
1	2	13	6 × 3.8	Not organized, edematous, hemorrhagic, no thinning of ventricular wall.
2	2	21	5 × 5½	Hemorrhagic, some organization in more basal part of infarct.
3	3	33	small	Not visible on epicardial surface. See table 2.
4	4	30	5 × 2.6	Ventricular wall thinned out.
5	4	23	5.8 × 2.3	Wound infection. Infarct presents some areas of necrosis, but also scar tissue.
6	7	14	4.5 × 3	Calcification. Ventricular wall thinned out to 2 mm.
7	9	9	3 × 2	Healed infarct.
			Cortisone Treated‡	
8	1½	30	5.7 × 4.0	Pneumonitis.
9	2	7	6.0 × 4.0	Ventricular wall thinned out, hemorrhagic areas.
10	2	13	5.5 × 5.5	Thrombus in coronary artery proximal to ligature. Mural thrombus in left ventricle.
11	2	19	—	Patchy necrosis, from site of ligature to apex. Not measurable. Some thinning of anterior left ventricular wall. Pericarditis.
12	4	23	4.0 × 3.0	Healed infarct. Ventricular wall thinned out.
13	4	16	5.5 × 2.5	Ventricular wall thinned out. Necrotic areas. Wound infection.
14	7	13	6.7 × 6.0	Pericarditis, ventricular wall thinned out to 1 mm. Largest infarct to date.
15	9	14	5.0 × 4.0	Stormy course. Pneumonia, numerous infections. Many thoracic adhesions. Ventricular wall thinned out to 1 mm.

* mm. from origin of artery.
† maximum length and width of infarct.
‡ 10 mg./Kg./day beginning six days before coronary occlusion and daily thereafter.

On microscopic examination, attention was given to the presence and extent of necrotic areas, the comparative concentrations of polymorphonuclear and mononuclear leukocytes, the number of fibroblasts and the extent to which fibrous tissue (scar) had been formed. The evaluation was done on a relative 0 to 4 plus basis.

Necrotic tissue had essentially disappeared from the myocardium of untreated dogs some-

control dog 5 (four weeks) also had some residual necrotic areas and a wound infection. On the other hand, it seems that infections do not necessarily delay the disappearance of necrotic areas since cortisone-treated dog 14 (seven weeks) had an active pericarditis, but his infarct was well healed and free of necrotic tissue. It cannot be said, therefore, that cortisone treatment directly delayed the disappearance of necrotic areas. It can be concluded,

however, that cortisone treatment did not reduce the size of the infarcts or promote the healing process.

Second Series. This series differed from the previous series in many respects: the cortisone dose was reduced from 10 to 3 mg. per kilogram; and, observations were made on the postoperative behavior and mortality.

No differences in postoperative activity or well-being were noted between the control and cortisone-treated dogs. All dogs exhibited their usual preoperative behavior. Our observations

TABLE 2.—*Microscopic Examination of Infarcted Areas of Hearts from Control and Cortisone-Treated Dogs*
First Series

Dog. No.	Myocardial necrosis	Connective tissue	Fibroblasts	Polymorphonuclear cells	Mononuclear cells	Comment
Controls						
1 (2 weeks)*	4+	0	2+	3+	2+	
2 (2 weeks)	4+	2+	3+	0	3+	
3 (3 weeks)	0	3+	1+	0	1+	Small healed infarct.
4 (4 weeks)	0	3+	1+	0	1+	Ca deposit. Healed infarct.
5 (4 weeks)	1+	3+	2+	0	2+	Wound infection. Fairly well healed.
6 (7 weeks)	0	3+	1+	0	1+	Healed infarct.
7 (9 weeks)	0	4+	1+	0	0	Healed infarct.
Cortisone Treated						
8 (1½ weeks)	4+	0	2+	0	2+	Pneumonitis.
9 (2 weeks)	2+	2+	2+	±	2+	Wound infection.
10 (2 weeks)	4+	1+	2+	1+	2+	Uneventful course.
11 (2 weeks)	4+	1+	2+	±	2+	Pericarditis.
12 (4 weeks)	0	4+	2+	0	2+	Healed infarct.
13 (4 weeks)	3+	1+	3+	0	3+	Concurrent wound infection.
14 (7 weeks)	0	3+	2+	0	2+	Healed infarct. Pericarditis.
15 (9 weeks)	4+	2+	3+	0	3+	Numerous infections. Pericarditis.

* Postoperative time.

injection was intramuscular rather than subcutaneous; the first injection was made at the time of coronary occlusion rather than as pretreatment for a six day period; dogs were sacrificed two weeks after coronary occlusion; all dogs received antibiotics prophylactically; do not coincide with those of Johnson and coworkers[1] who thought their cortisone-treated dogs were more active than the controls.

A total of 16 dogs were operated upon. Two dogs died during the first 24 hour postoperative period. One of these was cortisone-treated and

the other a control. No difference in mortality was observed, therefore. It should be pointed out, however, that the two-stage coronary ligation procedure was employed. This procedure was designed to reduce the mortality following acute coronary occlusion.[2]

Although surgical trauma was held to a minimum, some intrathoracic adhesions, usually visceral to parietal pleura, were observed in all dogs with one or two exceptions. No differences between the control and cortisone-treated dogs were observed. No intrathoracic infections were observed and only one minor wound infection occurred.

Table 3 presents the calculated volume of the infarcts in the control and cortisone-treated

TABLE 3.—*Comparison of the Volume of Infarcts in the Hearts of Control and Cortisone-Treated Dogs Second Series*

Control				Cortisone Treated			
Dog No.	Weight	Heart wt.	Volume of infarct	Dog No.	Weight	Heart wt.	Volume of infarct
	Kg.	*Gm.*	*cc.*		*Kg.*	*Gm.*	*cc.*
1	10.9	99.8	7.38	8	16.2	124.2	6.55
2	14.3	123.7	none	9	13.2	96.3	5.05
3	11.7	94.7	7.50	10	10.7	114.4	13.70
4	16.3	104.2	8.05	11	13.3	93.2	9.28
5	12.4	92.5	4.07	12	12.2	107.5	9.68
6	12.8	96.7	7.65	13	11.3	97.6	5.65
7	12.9	83.5	3.71	14	15.4	141.5	12.75
Av....	13.0	99.3	5.48		13.2	110.7	8.95

experiments. Although the average volume of the cortisone series appears to be appreciably larger than the average control volume (8.95 cc. vs. 5.48 cc.), there is no statistically significant difference between them. These data certainly do not suggest that cortisone treatment reduces the size of the infarct.

Since all observations were terminated two weeks postoperatively, the microscopic examination becomes particularly significant. In addition to the parameters examined in the previous experiment, an estimation was made of the degree of vascularity within the infarcted area. Table 4 shows the results of the microscopic examination. As in experiment 1 only the comparison of the areas of residual necrosis might indicate a significant difference between the two groups. However, the area of residual necrosis may be correlated with the size of the infarct. Correlation of infarct size (table 3) and extent of necrosis (table 4) suggests such a relationship. If so, then, since the average infarct size in the cortisone-treated group is larger, more residual necrosis could be expected, but, since the difference in average infarct size is not significant, the apparent difference in residual necrosis is not significant either.

TABLE 4.—*Microscopic Examination of Infarcted Area of Hearts from Control and Cortisone-Treated Dogs Second Series*

Dog No.	Myocardial necrosis	Vascularity of granulation tissue	Connective tissue	Polymorphonuclear cells	Mononuclear cells and fibroblasts
Controls					
1	4+	2+	3+	±	2+
2	—	— No infarction, normal		—	—
3	2+	2+	4+	2+	2+
4	1+	3+	3+	0	3+
5	0	0	±	0	1+
6	1+	3+	3+	0	2+
7	1+	3+	2+	0	2+
Cortisone Treated					
8	3+	2+	2+	0	2+
9	0	1+	1+	0	1+
10	4+	1+	1+	3+	3+
11	4+	2+	2+	±	2+
12	3+	2+	1+	1+	4+
13	2+	2+	3+	0	3+
14	3+	3+	1+	2+	3+

It is concluded that the second series, like the first, showed no effect of cortisone on the size of the infarct or its rate or mode of healing.

DISCUSSION

These results fail to confirm the claims made by Johnson, Scheinberg, Gerisch and Saltzstein.[1] No desirable effect of cortisone treatment on either the size of the infarct or its rate of healing was observed. Our results are similar to those reported by Chapman, Skaggs, Thomas and Green.[6]

Our postoperative mortality figures cannot be compared with those reported by Johnson and associates[1] because of the difference in the technic of coronary ligation. However, in view of the complete lack of confirmation of their main thesis and the fact that our studies do not indicate that cortisone increases the vascularity of the infarcted area, some question may be voiced concerning their mortality figures. Since, (a) acute mortality is due chiefly to ventricular fibrillation, (b) conditions leading to fibrillation are set up within one or two minutes after occlusion,[7] and (c) ventricular fibrillation usually occurs within 20 to 30 minutes after occlusion,[1] it is difficult to imagine how a relatively small dose of highly insoluble cortisone (acetate) administered intramuscularly at the precise moment of coronary occlusion could protect the ventricle from fibrillation. It may be, however, that cortisone protects from fatal ventricular fibrillation by inhibiting production of, or by destroying some toxic substance from the ischemic area.[8]

Summary

The effect of cortisone acetate (3 to 10 mg. per kilogram) on the size and healing of myocardial infarcts was studied in two series of dogs. The size of the infarct in the hearts of cortisone-treated dogs did not differ significantly from the untreated controls, nor were any striking differences detected by microscopic examination of the infarcted areas. It is concluded that cortisone treatment does not reduce the size of infarcts resulting from acute coronary occlusion.

Sumario Español

El uso de la cortisona profilacticamente o terapeuticamente no apareció tener efecto beneficioso alguno en reducir el tamaño de infartos del miocardio producidos por medio de ligación de la arteria coronaria en perros. No se notó diferencia significativa alguna entre los controles y los animales tratados con cortisona en cuanto respecta a la vascularidad y la cicatrización del infarto.

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Congenital Aneurysm of the Right Sinus of Valsalva, Diagnosed by Aortography

By WALTHER FALHOLT, M.D., AND GREGERS THOMSEN, M.D.

This paper contains a brief review of the cases, published earlier, of aneurysms of the sinuses of Valsalva, and a case is reported in which the diagnosis was made before rupture of the aneurysm by means of thoracic aortography. No reports are to be found in the literature of the diagnosis of unruptured aortic sinus aneurysms and of the associated clinical findings. Roentgenograms, aortograms and catheterization findings are included.

THE three sinuses of Valsalva, or aortic sinuses, form the proximal, partly intracardiac portion of the aorta. Congenital aneurysms, developing from the sinuses, are held by Abbott[1] to be caused by abnormal fusion of the aortopulmonary septum with the ventricular septum. This theory can only be applied to the aneurysms arising from the right and posterior sinuses. Micks[2] and Raman and Menon,[3] however, have described congenital aneurysms of the left sinus of Valsalva. The theory of Venning[4] that the aneurysms are due to defects in the elastic tissue of the sinuses, therefore, seems more plausible.

The rarity of aneurysms of the sinuses of Valsalva has been demonstrated by Schuster,[5] who in 3000 autopsies found two cases. Snyder and Hunter[6] among 5896 autopsies likewise found only two cases, and they stated that 10 aneurysms of the sinuses of Valsalva were found among 287 aortic aneurysms in 12,000 autopsies. The etiologic factors were maintained to be syphilis, atherosclerosis, and endocarditis. A group of cases was considered of unknown origin.

Abbott[1] in her review was able to find only 12 cases of congenital aneurysms in the literature. Morgan Jones and Langley[7] in their recent review collected 23 cases and added two cases of congenital aneurysm. Since then Venning has published three additional cases. Micks[2] reported a case of congenital aneurysm of all three sinuses of Valsalva and referred to three similar cases, published earlier.

Of the 33 cases published to date, 23 have developed from the right aortic sinus, five from the noncoronary sinus, one from the left aortic sinus, and in four cases aneurysms of all three sinuses were found. Depending upon the origin of the aneurysm, it extends into the interventricular septum or the wall of the ventricles or auricles. Other congenital abnormalities of the heart are often associated with the aneurysms, such as ventricular septal defect and bicuspid aortic valve.

Rupture of the aneurysm can occur at any time of life and is usually provoked by physical strain. While acquired aortic sinus aneurysms most frequently rupture into the pericardial sac,[8] the congenital aneurysms usually rupture into the right ventricle. Eight cases have been reported which ruptured into the right auricle, and single cases have been reported which ruptured into the pulmonary artery and left ventricle, respectively.

Before rupture of the aneurysm, no symptoms or uncharacteristic symptoms are present. In the case published by Herson and Symons[9] the patient was examined at the age of 12 years, several years before rupture occurred. A loud systolic murmur was heard over the whole precordium. X-ray examination showed no cardiac enlargement and the electrocardiogram was normal. Autopsy after rupture of the aneurysm 20 years later revealed that, besides an aortic noncoronary sinus aneurysm, a ventricular septal defect was present. The murmur was possibly attributable to the septal defect. In the case reported by Micks, a sys-

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tolic apical murmur was audible and roentgenograms showed enlargement of the heart.

Cardiac enlargement, prolongation of the auriculoventricular conduction time, and diastolic murmurs can probably be attributed to associated congenital abnormalities of the heart or complications due to progression of the aneurysm and encroachment on the conduction bundle, the pulmonary artery, the aorta, the auriculoventricular valves or the coronary arteries.[7] Ostrum and coworkers[10] by x-ray screening have observed intracardiac bulging caused by acquired aortic sinus aneurysms and have discussed similar bulgings in other conditions.

Rupture of the aneurysm produces an acutely critical situation with precordial or substernal pain, shortness of breath and feeling of weakness, often followed by collapse. After rupture into the right side of the heart, a systolic-diastolic murmur will develop, in some cases accompanied by a systolic, rarely a diastolic[1] thrill, with its maximum in the third and fourth left intercostal space. When, after an acute onset, a collapsing pulse is combined with evidence of pulmonary hypertension, shown by x-ray examination, a fistula between the aorta and the lesser circulation is suggested, as pointed out by Venning.[4]

The time of survival after rupture of the aneurysm into the right side of the heart has been described as varying from a few seconds[11] to 17 years.[7] The oldest patient in whom rupture of a congenital aortic sinus aneurysm has been reported was 64 years of age. Death after rupture is caused by heart failure.

Bacterial endocarditis is maintained to have been the cause of death in six cases of congenital aneurysm. Jones and Langley suggest that when bacterial endocarditis develops in a heart apparently previously healthy, an aneurysm of the sinus of Valsalva must be suspected. In the case reported by Micks, heartblock was the cause of death.

No reports are to be found in the literature of the diagnosis of unruptured congenital aortic sinus aneurysms during life. Based upon the history of an acute onset, a continuous murmur, evidence of pulmonary hypertension, and a collapsing pulse, Venning made the diagnosis of a ruptured aneurysm of the sinus of Valsalva during life. The differential diagnosis of the condition being discussed and aortic septal defect and even patent ductus, however, can be of great difficulty. If rupture of the aneurysm has taken place into the outflow tract of the right ventricle or into the pulmonary artery, cardiac catheterization will be of no great help, unless the ductus or aortic septal defect are directly catheterized, since the physiologic conditions will be the same in any of these instances.

The performance of aortography after introduction of a cardiac catheter into the ascending aorta has greatly widened the possibilities of studying the anatomy of the aorta in the living subject. In the case to be reported, aortography was made by the technic developed by Broden and associates.[12]

Case Report

A 17 year old girl from Iceland was referred to us by Dr. S. Samuelsson, of Reykjavik, because of cardiac complaints. She gave no family history of cardiac disease; there was no history of syphilis and clinical examination revealed no symptoms of congenital syphilis. At 1 year of age she had had a severe attack of measles but had suffered from no other infectious diseases. Her physical abilities had always been diminished, compared with that of her contemporaries, because of dyspnea and palpitations. At school she was not able to take part in gymnastics. Cyanosis was never observed, and there had been no attacks of precordial pain or severe dyspnea. The diagnosis of congenital heart disease was made at the age of 13 years.

Half a year before admission to the hospital she had been employed drying codfish which involved lifting heavy boxes of fish. Because of dyspnea and palpitations she had to give up this work. She suffered no discomfort from walking or climbing stairs.

Her height was 163 cm. and weight, 54.4 Kg. The temperature remained normal during her hospitalization. The blood pressure in an arm was 130/90. Her intelligence was normal. There was no cyanosis of the skin and mucous membranes, and no dyspnea at rest. The lungs were free of abnormality on examination.

The apex beat was palpable in the fifth intercostal space 1 cm. lateral to the midclavicular line. A systolic blowing murmur, grade 2, and a short protodiastolic murmur were audible at the apex. The intensity of the murmurs increased toward the sternum, and in the left third and fourth intercostal space there was a continuous murmur similar to

that of a patent ductus, though of higher frequency. In the right fourth intercostal space the diastolic murmur was dominating, harsh in character and peculiarly superficial. The murmurs were weak, though audible in the second intercostal space to the right of the sternum. There was a weak systolic thrill with its maximum in the fourth space to the left of the sternum. No transmission of the murmurs to the arteries in the neck was observed. The pulse was considered normal. A faint pistol shot sound was audible over the femoral arteries. There was found no evidence of capillary pulsation nor clubbing of the fingers. The liver was not palpable. No edema was present.

The sedimentation rate was 8 mm. in 1 hour, the hemoglobin 95 per cent and the red blood cell count 4.18 million. The hematocrit was 36 per cent. The antistreptolysin titer was found to be 160. The Wassermann and Kahn reactions were negative. The basal metabolic rate was 102 per cent. No abnormal constituents were found in the urine.

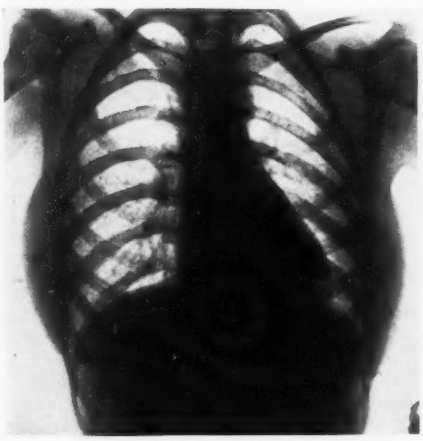

FIG. 1. Roentgenogram in the anterior-posterior view.

Electrocardiograms showed regular rhythm and a rate of 70 per minute. The P-Q interval was 0.16 second and the QRS interval was 0.08 second. In all standard leads the R wave was of highest voltage; in lead I, 18 mm., and in lead III, 7 mm. in height. The unipolar limb leads showed a semivertical heart. The precordial leads gave normal tracings.

Roentgenograms showed the heart to be normally shaped; the cardiac index was 12/24. The left ventricle was slightly enlarged. The vascular markings in the lungs were normal (fig. 1).

Oximetry demonstrated no abnormal fall in arterial saturation during three minutes of exercise (405 kilogram-meters per minute).

Cardiac catheterization* showed the following findings. Pressure in the pulmonary artery was 22/9 mm. Hg, in the right ventricle 22/0, and the mean pressure in the right auricle was zero. The oxygen saturation in the superior vena cava and the right auricle was 74 per cent, and in the pulmonary artery 75 per cent. The arterial saturation, determined by the van Slyke method, was 94 per cent. No evidence of shunts was found. The catheterization revealed no explanation of the cardiac symptoms.

Aortography: Under nitrous oxide oxygen-ether anesthesia, 60 cc. of 70 per cent Diodon were injected through a number 9 cardiac catheter, which was introduced into the ascending aorta via the right radial artery. Twenty aortograms in the right and left position were taken within 10 seconds.

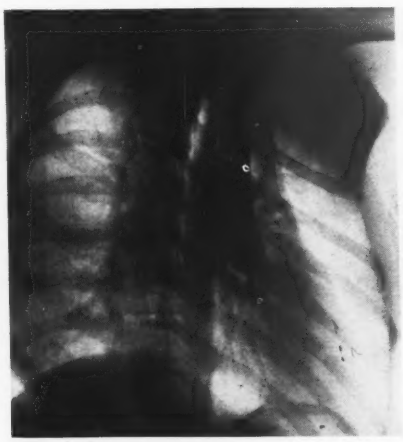

FIG. 2. Aortogram in the right oblique position

The aortic valves are rather sharply outlined. A narrow band of contrast substance is seen, extending from the aortic valve into the outflow tract of the left ventricle where the contrast disappears. This must be an expression of insufficiency of the valve.

A rounded shadow of contrast about the size of walnut appears below and a little in front of the aorta. A thin connection is seen, extending from the right aortic sinus to the shadow previously described. After its disappearance from the aorta, dye is still seen to be retained in the area of this shadow. No evidence of emptying of the dye into the lesser circulation is found.

Conclusion: A chamber below and a little in front

*Pressures were recorded by means of the electrical condenser manometer of Hansen.[16] The oxygen saturation of the blood samples was determined by the Brinkman and Zylstra[17] hemoreflectometer. The oxygen capacity was determined by the van Slyke apparatus.

of the aorta, but situated deeply in the heart shadow, has been demonstrated. This chamber is only in communication with the aorta. It is undoubtedly an unruptured aneurysm of the right sinus of Valsalva. Furthermore, evidence of insufficiency of the aortic valve has been found (figs. 2, 3 and 4).

FIG. 3. Aortogram in the left oblique position

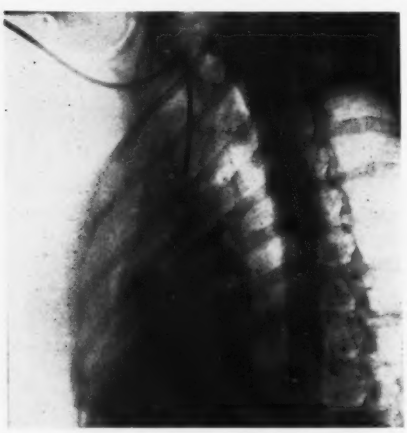

FIG. 4. Aortogram in the left oblique position, taken four seconds later than those in figures 2 and 3. Dye is still seen to be retained in the aneurysm.

DISCUSSION

No definite diagnosis was made on the clinical findings in the case reported. Based upon the location and character of the murmurs, the diagnosis of an aortopulmonary fistula, possibly an aortic septal defect, was entertained. The roentgenograms and catheterization findings did not support this diagnosis, as there was no evidence of pulmonary hypertension nor of an arteriovenous communication within the heart or involving the pulmonary artery. Aortography proved the presence of an unruptured aneurysm of the right sinus of Valsalva and an insufficiency of the aortic valve.

Aneurysms developing in the area under discussion could be either of the right aortic sinus or the right coronary artery. The congenital saccular aneurysms of the right coronary artery develop from the points of partition of the artery, usually 0.5 to 2 cm. distal to the sinus of Valsalva.[18] These aneurysms are located on the surface of the heart. In the case reported, the aneurysm, like an aortic sinus, is deeply buried in the musculature of the heart, and a fistula from the sinus of Valsalva to the aneurysm can be followed on aortograms.

It seems reasonable to explain the murmurs found in this case as resulting from the intracardiac location of the aneurysm. During contraction of the heart muscle, the aneurysm will be partially compressed and, since no rupture of the aneurysm was found, blood will pass from the aneurysm into the aorta during systole. After relaxation of the muscle, blood will pass from the aorta into the aneurysm during diastole. In this way a systolic-diastolic murmur is produced. The murmur caused by the associated insufficiency of the aortic valve would be of another location and character than the one described in the previous section.

Murmurs, similar to the ones found in our case, have been reported in earlier published descriptions of aortic sinus aneurysms. The peculiar impression of the superficial location of the murmur has been described by Abbott and by Jones and Langley. In their cases, the aneurysm, in contrast to the present one, had ruptured. Consequently the aneurysm would have emptied into the right side of the heart during systole, and have been refilled from the aorta during diastole.

Insufficiency of the aortic valves, according to the literature, is a frequent accompaniment of congenital aneurysms of the sinuses of Valsalva. It can be due to congenital abnormality of the aortic valves, bicuspid valves, or encroachment by the aneurysm on the valve or outflow tract of the left ventricle.

The opinion that our case is of congenital origin is based upon exclusion of the known causes for the development of acquired aneurysms of the sinuses of Valsalva. There was no evidence of either congenital or acquired syphilis; the patient had had no serious infectious diseases; examination of the arteries revealed no signs of premature arteriosclerosis; and kymograms showed normal pulsations of the aorta.

Summary

The clinical, prognostic and pathologic experiences from cases of congenital aortic sinus aneurysms, published earlier, are briefly reviewed and the embryology discussed.

In a 17 year old girl a case of congenital aneurysm of the right sinus of Valsalva was diagnosed by aortography. A report is given on the history and the clinical findings. Roentgenograms and cardiac catheterization rendered no help in establishing the diagnosis.

The diagnostic problems and origin of the murmurs in the case reported are discussed.

Sumario Español

Este trabajo contiene un breve repaso de los casos de aneurismas de los senos de Valsalva y se informa un caso en el cual el diagnóstico se estableció antes de la rotura del aneurisma por medio de aortografía torácica. En la literatura no se encuentran informes de casos diagnosticados antes de la rotura del aneurisma en aneurismas del seno de Valsalva ni de los hallazgos clínicos relacionados. Radiografías, aortogramas y hallazgos de cateterismo se incluyen.

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Electrocardiographic Leads

I. Introduction

By Richard McFee, M.S., and Franklin D. Johnston, M.D.

This paper is the first of a series of three which will deal with the relationship between the voltages in electrocardiographic leads and the electromotive forces of the heart. The general purpose of this series is to discuss various experimental and theoretic technics which can be used in the analysis of a given lead, and in the building up, or "synthesis," of leads having desired characteristics. The procedures used are based on a fundamental theorem which takes into account not only the irregular shape and conductivity of the body but also the spatial dispersion of the electromotive forces within the heart. It is closely related to the "lead vector" concept of Burger and van Milaan.

In this first paper the basic definitions and theorems are developed. The second paper discusses various methods of analyzing leads. The third and last presents a number of systematic procedures for designing leads, both vectorcardiographic and unipolar. Such leads can have substantially higher accuracies than those now in use, because their design takes into account the shape and conductivity of the body and its tissues, and the eccentric and extended location of the heart.

FOREWORD

By Frank N. Wilson, M.D.

THE basic principles which have led to a progressively better understanding of the factors that determine the form of the electrocardiogram were known over 30 years ago. Seventy years had passed since Helmholtz, with the experiments of DuBois Raymond in mind, stated and proved a number of theorems bearing on electrical currents in volume conductors. Waller's work with the capillary electrometer in 1889, and his crude conception of the cardiac dipole, had been supplanted by the string galvanometer and the manifest vector of Einthoven and his associates. His, Tawara, Keith and Flack had furnished an accurate description of the specialized cardiac tissues, and Lewis had made an extensive and accurate study of the spread of the excitatory process over auricular and ventricular muscle, had introduced unipolar direct leads, and had advanced the theory of limited potential differences which amounted in essence to what was subsequently referred to as the "dipole hypothesis."

Unfortunately, the application of the long known and well understood principles of potential theory to electrocardiography was not in general well received. Many of the more or less theoretic and mathematical papers along these lines aroused a storm of opposition. Some of the criticism came from physicians who felt that electrocardiography was a purely empiric science and that progress in the field could come only from comparison of the electrocardiographic findings with clinical and postmortem data. Much opposition came from the physiologists, many eminent in their field, who not only discounted any article of a theoretic nature but also regarded the dipole hypothesis as rank heresy.

Despite this opposition, the application of electrical principles to electrocardiography has continued, and the simpler approximations of the early years are now being replaced by more accurate and sophisticated analyses. It is astounding that almost all the recent theoretic advances are based on principles which were stated and proved by Helmholtz a century ago. His work was the result of his interest in the studies of Emil DuBois Raymond on injury currents of tissues. These were published in 1847. At the time Helmholtz wrote, too little was known about bioelectric currents to make his theorems of much practical importance in this field, and apparently they were forgotten before knowledge of this subject had advanced to the point where they were most needed.

The fundamental principles stated and explained by Helmholtz may be considered under three headings: (1) The Principle of Superposition, (2) The Principle of the Electromotive Surface and (3) The Principle of Reciprocity. The first of these has been made the basis of the concept of the "lead vector" of Burger and van Milaan. The second has been used as a means of finding the field of an eccentric dipole in a sphere. Many of the applications of the third principle of Helmholtz, the "reciprocity theo-

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'em," are considered in the following three papers by McFee and Johnston. Their discussion of the implications of this basic theorem may prove to be one of the most interesting contributions to the understanding of the electrocardiogram that has been made in many years.

(*This Foreword was written by Dr. Wilson in the winter of 1951 shortly after he had read and edited the first paper of the series. Before his death he had also read and commented on the second paper and had become familiar with a number of the topics taken up in the third. Many of the ideas presented in the papers were developed during discussions with him at his farm. There is no question that the work would not have been done had it not been for his invaluable suggestions, fellow interest and consistent and good humored encouragement.*)

OUR understanding of the manner in which the electromotive forces of the heart produce voltages in electrocardiographic leads has been greatly advanced in recent years through the introduction of the concept of the "lead vector" by Burger and van Milaan.[1] This concept, which stems from basic electrical principles, has enabled us to consider, for the first time, the relation between a cardiac electromotive force and the voltage produced by it in a given lead, with due regard for the irregular shape and nonhomogeneous electrical conductivity of the body. Electrocardiographic studies employing this concept are free from nearly all the objections which have been raised against mathematical studies which assume that the body is an infinite homogeneous conductor.

However, as might have been expected, the relation between the electromotive forces of the heart and the lead voltages has not been completely clarified by the concept of the lead vector. The main reason for this is that it assumes that the electromotive forces of the heart may be regarded as originating at a point and, of course, this is not actually the case. In fact, it is their dispersion that accounts for the special interpretation given to the chest leads. Burger and van Milaan were quite conscious of this, and drew special attention to it in their papers. Subsequent experiments by Wilson, Bryant and Johnston,[2] and by den Boer[3] have indicated that the influence of this dispersion is by no means negligible. However, the difficulty of dealing practically with this spread of the cardiac forces, of analyzing and building up leads with it in mind, has remained.

The method of studying electrocardiographic leads that is advanced in this series of papers is the outgrowth of an attempt to solve this problem. This has been done by replacing the concept of the lead vector with one closely related to it, that of the "lead field."

The "lead field" is the electric field set up in the body when a unit current is introduced into the lead. The relation between it and the lead vector is an extraordinarily simple one. At any point in the heart the lead field *is* the lead vector with respect to electromotive forces arising at that point. The two concepts are similar in many respects. Just as Burger and van Milaan analyzed leads by finding the lead vectors, leads are analyzed here by finding the lead fields. Similarly, in place of the synthesis of leads having prescribed vectors, as is done in the universal vectorcardiograph of Becking, Burger and van Milaan,[4] methods are worked out here for the synthesis of leads with prescribed fields.

It is a surprising fact that the concept of the lead field, although more general and useful than that of the lead vector, is nevertheless easier to understand and to use. The reason for this is that the lead field is not, like the lead vector, a mathematical concept. The studies on fluid mappers, recently reported by McFee, Stow and Johnston,[5] demonstrate this quite clearly. The answers to many puzzling electrocardiographic questions become immediately obvious, without any mathematics, after one has grasped the basic significance of these fields in relating the voltages of the lead to the electromotive forces of the heart. It is only when one wishes to be exact that the necessity for the use of mathematics arises.

It is convenient to divide the presentation of this viewpoint into three parts: (a) definitions and theorems, (b) lead analysis, and (c) lead synthesis. A special attempt has been made to state the definitions and theorems in an unambiguous and clinically meaningful form, and to develop them in a compact and systematic way.

The first paper, in addition to deriving basic theorems concerning lead fields, shows how

the definitions of the "dipole moment" and the "potential," which arose in connection with the analysis of fields in infinite homogeneous media, may be applied to the human body. Following this, a simple definition of the accuracy of an interpretation of a lead is worked out. Using it, the difference between remote and local leads is discussed, in the hope of correcting the view, recently advanced by several authors,[6, 7] that the voltages produced in local leads are the same as those produced in remote leads, except that their magnitude is greater.

The second paper of this series concerns the analysis of leads in terms of their fields. Many experimental technics for determining these "lead fields" will be pointed out, and practical examples given. The possibility of "null leads," which are insensitive to electromotive forces at some point within the heart, are touched upon. In addition, some of the outstanding electrocardiographic problems requiring the analysis of leads are discussed.

The third and last paper considers the problem of constructing leads having desired characteristics; that is, lead fields of certain types. Approximate, practical methods of designing such leads are worked out first, and used to find fairly simple vectorcardiographic leads, which are somewhat better than those now employed. These leads are constructed by connecting many electrodes to the two terminals of the lead by resistors of appropriate sizes. They are essentially a generalization of the resistor leads recently studied by Wilson and his associates.[2] Simple improvements for the central terminal are also presented, along with methods for constructing variable leads (rotators) capable of selecting a desired component of the heart vector. In addition, the theoretic problem of obtaining "perfect" leads is treated in some detail. It is shown that they are possible in certain cases where the conductivity variations within the body are fairly simple. Finally, it is shown that the potential anywhere *in* or *on* the body (but outside the heart), as measured to a "perfect" indifferent electrode, can be found from measurements of the potential differences at the *surface* of the body, assuming only that the heart is spherical and homogeneous, and that the tissues outside the heart are homogeneous also.

It is quite interesting to note that the importance of the lead field, which suggested itself here as a means of generalizing the lead vector concept, was recognized and emphasized by Helmholtz[8] over 100 years ago. The great significance of these fields is based upon the reciprocity theorem, whose potential importance in electrocardiography was emphasized recently by Wilson, Bryant and Johnston.[2] In recent years the possibility of using such fields in studying electrocardiographic leads has suggested itself to several investigators in addition to the present authors. Lepeschkin,[9] in his consideration of the "tubes or lines of flow of a lead" is actually dealing with lead fields. Isopotentials of lead fields have been traced not only by Wilson, Bryant and Johnston,[2] but also by Schmitt.[10] Schmitt was apparently the first to construct rotators, although similar and less elaborate circuits have been built independently not only by the author but also by McKay, Romans, Brody and Little.[11]

The general purpose of this series of papers is to show how the basic principles of electrical theory may be used to study the relation between the electromotive forces of the heart and the voltages produced by them in electrocardiographic leads. The relations between these electromotive forces and the electrochemical and physiologic processes of the cardiac muscle, and between the latter and clinical diagnosis, although of equal importance, seem best treated as separate problems. For this reason, such considerations are omitted. It is to be hoped that a better understanding of all these relations will eventually result in substantial improvements in the reliability of electrocardiographic interpretations.

Definition of a Lead and of an Electromotive Vector

We are concerned here with the study of the relationship between the electromotive forces of the heart and the voltages produced by them in the different leads. Precisely what

do we mean by a "lead" and how can we describe an electromotive force?

The term "lead" was used by early electrocardiographic investigators to refer to a single pair of electrodes attached directly to the body. However, certain generalizations of this original use of the word have appeared in recent years. A central terminal chest lead, for example, has only one electrode attached directly to the body. The other terminal of this lead is connected to it only indirectly; that is, via resistors. In view of this use of the term, it would seem reasonable to define a lead as any pair of terminals, each connected to the body either directly or indirectly through any number of resistors.

However, even this broad use of the word might be objected to, because it does not include the "leads" which result from adding together the outputs of several vacuum tube amplifiers whose inputs are connected to electrodes attached to the body. What is the difference between leads of this type and the leads formed by connecting two terminals to the body via resistors? A simple theorem, which will be proved later, furnishes us with the answer. It states that no matter how many vacuum tube amplifiers are used, the same voltage can be obtained with a single "resistor lead" and one amplifier. This theorem insures that the following definition is a completely general one: *A lead is a pair of terminals, each connected either directly or with any number of resistors to electrodes on the body.* The resistances should be large enough that the connection of the lead to the body does not alter the electric field. To avoid ambiguity, one terminal of the lead will arbitrarily be called its "positive" terminal, and recording voltmeters should be connected so that their deflection has a positive sense when this terminal is electrically positive relative to the other.

The electromotive forces of the heart may be thought of either as electromotive surfaces such as exist between the metal and electrolyte in ordinary batteries, or as extended volume gradients such as occur when dissimilar solutions diffuse into one another. In any case, these two viewpoints are by no means incompatible; a volume gradient can be simulated by a large number of weak electromotive surfaces piled one on top of the other, and conversely, an electromotive surface can be treated as a very intense localized volume gradient.

So far as subsequent developments in these papers are concerned, it would not matter which of these viewpoints were chosen as a starting point. In fact, it would be possible to get along without either of them. This could be done by describing the electromotive forces "operationally," using miniature leads, in such a fashion that nothing is said or implied about the nature of the electromotive forces or the way in which they are generated. However, this approach, although rigorous, would be a very dreary one. For this reason, the most attractive approach has been chosen, and it is assumed here, purely for convenience, that the electromotive forces of the heart exist as electromotive surfaces.

One advantage to this assumption is that it fits in neatly with the theoretic work of Helmholz on electromotive forces in volume conductors. Another advantage is that it is in agreement with the bulk of experimental and theoretic studies on cardiac electrophysiology. These studies indicate that the electromotive forces are located at the boundry between resting and active tissue, where they form an electromotive surface whose positive side is next to the resting tissue.

An electromotive surface of this sort may be described quantitatively by breaking it up into a number of small elements, each being essentially flat and having a uniform potential difference. The magnitude of the electromotive force of each of these elements can be specified in terms of the "electromotive vector" of the element, which is defined as follows:

The electromotive vector, $\vec{e}$ of any small element of an electromotive surface is a vector which points in the direction faced by the positive side of the element and which has a magnitude equal to the potential difference across the element multiplied by its area.

Note that the dimensions of the components of this electromotive vector are volts times area.

An element of an electromotive surface can be simulated in an electrolytic bath with

several pieces of nonpolarizing metal foil and a battery. The pieces of foil are placed back to back with a thin layer of insulation between them and each piece of foil is connected to a terminal of the battery. The net effect of an artificial element of this sort is indistinguishable from that of an element of a physiologic electromotive surface having the same area and potential difference.

The Lead Field

Using the specific definitions of a "lead" and "electromotive force" which have just been given, with the reciprocity theorem of Helmholtz,[8] it is not difficult to see how the influence of the electromotive forces on the lead voltages may be found by studying the fields of the leads.

In his derivation of the reciprocity theorem, Helmholtz was considering the effect of an electromotive surface in a volume conductor on the deflection of a galvanometer connected to that conductor. He stated his theorem in the following way: "Every single element of an electromotive surface will produce a flow of the same quantity of electricity through the galvanometer as would flow through that element itself if its electromotive force were impressed on the galvanometer wire. If one adds the effects of all the electromotive surface elements, the effects of each of which are found in the manner described, he will have the value of the total current through the galvanometer."*

To see more clearly what this theorem means in electrocardiography, consider the effect of each individual element of an electromotive surface within the heart on the deflection of a galvanometer connected to a lead. This situation is illustrated by the example shown in figure 1*A*. Here e is the potential difference across the element and I is the current it produces in the lead. According to the reciprocity theorem, a battery with the same voltage put in series with the lead would cause the flow of the same current through the element. In this case, if the voltage of the battery were twice as great, naturally the resulting current also would be twice as great. In general, if the voltage of the battery in series with the lead is E and the resulting current which flows through the element is i (fig. 1*B*), then the reciprocity theorem requires that

$$E/e = i/I \tag{1}$$

By transposing terms, this equation may be rewritten as

$$I = ie/E \tag{2}$$

This last equation enables us to determine the current which flows through the electrocardiographic measuring apparatus as the result of the electric field of the element of the electromotive surface. However, since electrocardiographs are so calibrated that they measure voltage rather than current, it is desirable to rewrite equation 2 so that it furnishes the open circuit voltage, v, rather than the current, i, of the lead. To do this, one must first recognize that the current, I, (fig. 1*A*) is related to the open circuit voltage, v, by the equation

$$I = v/R \tag{3}$$

where R is the sum of the resistance of the galvanometer and the resistance seen "looking into" the lead. This same resistance, R, also relates the current, I', (fig. 1*B*) which flows in

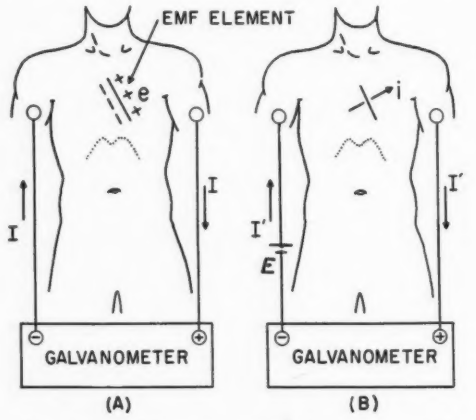

Fig. 1. Illustrates the reciprocity theorem. If E is equal to e, then i is equal to I. See text.

* The authors are indebted to Dr. Frank N. Wilson for this unusually clear and concise translation.

the lead to the voltage, E, of the battery which produces it. The equation here is

$$I' = E/R \tag{4}$$

If the values of I and E in these two equations are substituted into equation 2, then the R factor cancels, and

$$v = e(i/I') \tag{5}$$

Finally, if the voltage, E, is adjusted so that the current, I', flowing into the lead is unity, then this last equation becomes

$$v = ei \tag{6}$$

and this is the equation we seek. It says that every element of an electromotive surface within the heart will produce an open circuit voltage, v, in a given lead equal to the potential difference, e, of this element multiplied by the current, i, which passes through it as the result of connecting the lead to a unit source of current. If this current enters the negative terminal of the lead and leaves its positive terminal, then the voltage, v, will be positive if the current through the element enters the negative face and leaves the positive.

When the effects of all the elements of the electromotive surfaces are added together, the following fundamental theorem results: *The open circuit voltage, v, produced in any lead is related to the electromotive forces of the heart by the equation*

$$v = e_1 i_1 + e_2 i_2 + \cdots \tag{7}$$

where the e's are the potential differences of the electromotive force elements, and the i's are the currents passing through the elements when a unit current is introduced into the lead. The sum is extended to include all electromotive force elements of the heart. As was just mentioned, the products ei here will be positive if the current leaves the positive face of the elements, and negative if it enters the positive face. This field of current, which is produced in the body when a unit current enters the negative terminal of a lead and leaves its positive terminal, will henceforth be called its "lead field."

As an example of the practical value of this theorem, let us attempt to find the effect of a closed electromotive surface of uniform voltage on a lead whose electrodes are external to it. Since the potential differences of all electromotive force elements of this surface are the same, the voltage produced in the lead will, by equation 7, be equal to this voltage times the total lead field current which passes through the surface. But this current will be zero, since the lead electrodes are outside the closed surface, and any current entering the surface must, therefore, leave again somewhere else. Thus, we see that a closed electromotive surface of uniform potential difference will produce no voltage in a lead whose electrodes are all outside of it, and that this is true not only for the infinite homogeneous conductor, but also for any resistive conductor.

The Lead Vector

When a unit current is introduced into a lead, the resulting flow of current throughout the body will have a certain intensity and direction at every point in the body. That is, the flow of current forms a "vector field." Its magnitude and direction at any point can be represented by the symbol $\vec{J}$. (The magnitude of $\vec{J}$ is here taken as the current density, in current per unit area, at the point in question.) Now let us consider the relation between this vector field and the current passing through a specified element of the electromotive surface. If this element is sufficiently small, it will be effectively flat, and the magnitude and direction of the current passing through it will be the same at all points on it. The total current going through the element will then be equal to the component of the current field perpendicular to the surface of the element multiplied by the area of the element. Thus the voltage produced in the lead by that element will, by equation 6, be equal to the component of current perpendicular to the face of the element multiplied by the area of the element times its potential difference. If we now use the definition of the electromotive vector of such an element, which was previously given, and the mathematical definition of a "dot," or scalar

product,* it follows that equation 6 can be rewritten as

$$v = \overrightarrow{J} \cdot \overrightarrow{e} = J_x e_x + J_y e_y + J_z e_z \quad (8)$$

where the subscripts indicate components in the x, y and z directions.

If this equation is now compared with equation 1 in the first paper on "Heart Vector and Leads" by Burger and van Milaan,[1] it will be seen that the two, except for the symbols used, are identical. This means that *the current field, $\overrightarrow{J}$, at a point in the heart, resulting from the introduction of a unit current into the lead, has the same direction and intensity as the Burger lead vector of that lead with respect to electromotive forces located at that point.*

Equation 7, it should be noticed, can now be rewritten as

$$v = \overrightarrow{J_1} \cdot \overrightarrow{e} + \overrightarrow{J_2} \cdot \overrightarrow{e} + \cdots \quad (9)$$

In this more general form, the lead equation 8 of Burger and van Milaan can be used to study all types of leads and distributions of electromotive forces, rather than just vectorcardiographic leads and electromotive forces at a single point. However, it is clear that much more insight into the nature of leads will be gained if we replace the algebraic concept of the lead vector with the essentially geometric and physical concept of the lead field. For example, in terms of the lead field, it is easy to see why electromotive forces having certain directions produce no voltage in the lead, and why they produce a maximum voltage when facing at right angles to these directions. Furthermore, the relation between lead vectors in different parts of the heart, formerly obscure, becomes quite obvious in terms of lead fields. For these and many other reasons, the idea of the lead field, rather than the lead vector, will be used in these papers as the basic tool for studying electrocardiographic leads.

The Dipole Moment

The concept of the dipole moment is often based on the analysis of the electric fields produced in an infinite homogeneous media at large distances from the charges or electromotive forces generating the fields. This analysis shows that although in the neighborhood of these forces the variations in potential may be quite irregular, as the distance from the forces increases these variations become much simpler, and at large distances the field becomes exactly identical to that which would be produced by a single electromotive element of appropriate magnitude and direction located within the surface enclosing the actual complex cluster of electromotive forces. This equivalent electromotive force is known as the "dipole moment" of the cluster.

Using the concept of the lead field, it is easy to show that such an equivalent electromotive force exists, and to find a formula for it. Consider a lead formed by one electrode remote from a cluster of electromotive surfaces in an infinite homogeneous conductor, and a second electrode at "infinity." When a current leaves the conductor through the remote electrode and enters it through the electrode at infinity, the current lines in the neighborhood of the former will have the distribution shown in figure 2*A*. The small pear-shaped object in the figure is the region representing the heart, where the electromotive forces are located. It is clear that the flow lines of the current in this "heart" will have the appearance shown in figure 2*B*; that is, they will be for all practical purposes parallel. Since the resistance of the medium is uniform, this means that the current field throughout the "heart" will be uniform; that is, $\overrightarrow{J}$ has an unvarying magnitude and direction. To see what this would mean, consider equation 9. If $\overrightarrow{J}$ is a constant, this equation may be rewritten as

$$v = \overrightarrow{J} \cdot (\overrightarrow{e_1} + \overrightarrow{e} + \cdots) = \overrightarrow{J} \cdot \overrightarrow{H} \quad (10)$$

where

$$\overrightarrow{H} = \overrightarrow{e_1} + \overrightarrow{e_2} + \cdots \quad (11)$$

It is clear from equation 10 that a single electromotive force, of magnitude and direction $\overrightarrow{H}$ located anywhere within the heart, would produce the same voltage in this lead as the actual complex cluster of electromotive forces. The same argument applies to a lead

* This product is discussed on pages 13, 14 and 16 of reference 2.

from any other remote point to infinity, the equivalent electromotive force in all cases being that given by formula 11. What this formula essentially states is that *the dipole moment is equal to the sum of the electromotive vectors of all the elements of the electromotive surfaces.* That is to say, the dipole moment tells us the direction and magnitude of all the electromotive vectors acting together. It is

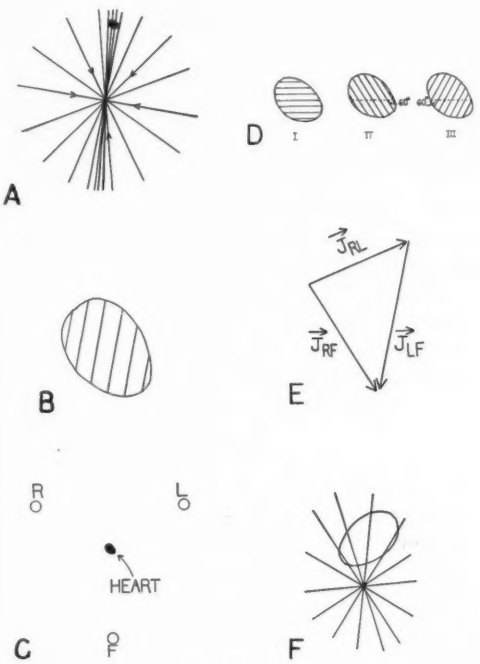

FIG. 2. See text

similar to the resultant of a number of mechanical forces acting together.

Using the concept of the lead field in conjunction with Einthoven's idealized assumptions, it is not difficult to derive his triangle scheme. Consider his model of the body, where the three lead electrodes in the infinite homogeneous conductor are arranged in an equilateral triangle centered in the heart. This arrangement is shown in figure 2*C*. It is clear from the symmetry of the leads with respect to the heart that the lead fields in the heart of leads *I*, *II* and *III* have the flow patterns shown in figure 2*D*. Since the lead vectors all have the same intensity, the lead vectors $\vec{J}_I$, $\vec{J}_{II}$ and $\vec{J}_{III}$ will form an equilateral triangle if drawn on a piece of paper. The voltage in each lead will be the scalar product of the dipole moment and the side of this triangle representing the lead. Since the lengths of these sides are all the same, this product will be the projection of the dipole moment on the side multiplied by some constant equal for all the sides. This, of course, is the basic principle of the Einthoven triangle scheme.

If, on the other hand, the three electrodes are not arranged in an equilateral triangle, but nevertheless are remote from the heart, the fields produced by them will still be uniform within the heart, but will have varying magnitudes and directions. If the fields associated with leads between any two pairs of the electrodes are known, the field associated with the one remaining pair is also known, since it can be considered to be the superposition of the fields of the first two. For example, if the three lead electrodes are *R*, *L* and *F*, and if the lead field associated with lead *RL* is $\vec{J}_{RL}$, and the field associated with lead *LF* is $\vec{J}_{LF}$, then the field associated with lead *RL* will be given by

$$\vec{J}_{RF} = \vec{J}_{RL} + \vec{J}_{LF} \qquad (12)$$

since the superposition of the lead fields of *RL* and *LF* will result in no current flowing into (or out of) the *L* electrode, a current of 1 ampere flowing out of the *R* electrode, and a current of 1 ampere flowing into the *F* electrode; that is, the introduction of 1 ampere into lead *RF*. This means that the three lead vectors will add together in the fashion illustrated by the example in figure 2*E*, and that these three lead vectors will therefore form a triangle. This illustrates how the lead field concept leads to the "Burger" triangle.*

THE HEART VECTOR

The electromotive forces of the heart, however, exist in a medium that is neither infinite

* This same argument applies regardless of the nature of the conductor or the location of the electrodes, provided that the lead vectors at only one point are considered.

nor homogeneous. Its resistivity varies not only from organ to organ, but also with the direction of the current flow. In these circumstances, then, how is it possible to use the concept of the dipole moment, and to find its components by measuring voltages at the surface of the body?

A great deal of confusion has arisen in connection with this problem. Attempts have been made to define a "heart vector" for the body in the same way that the dipole moment is defined for the infinite homogeneous medium; that is, in terms of the potential differences on the body surface remote from the heart. Unfortunately, it is a simple fact that there is *no* equivalent electromotive force which, located anywhere in the heart, will produce the same voltages at points remote from the heart that the actual electromotive forces do. For this reason, it is necessary to define the heart vector in some other way.

From the clinical point of view, the vector we are interested in is the same vector that would represent the dipole moment of the heart if its electromotive forces existed in an infinite homogeneous conductor. Of course they do not, but that does not prevent us from making the following definition. *The heart vector is the dipole moment which would be associated with the electromotive forces of the heart if they existed in an infinite homogeneous conductor. That is, it is the vectorial sum of the electromotive vectors of the heart.*

This definition may look at first like a rather useless one, since it is clearly impossible to remove the electromotive forces from the heart and place them in an infinite homogeneous conductor. However, our only purpose in doing this would be to measure the voltages produced there, and to use these measurements to calculate the dipole moment. This impossible operation might be bypassed then, if leads could be found whose fields in the heart are the same as those of leads in an infinite homogeneous conductor. That is, if the electromotive forces are the same and the lead field where they are located is the same, then by equation 9 the lead voltage will be the same. Since in an infinite homogeneous conductor a lead whose field within the heart is uniform will have a voltage produced in it proportional to the component of the dipole moment in the direction of the field, it follows then that *any lead connected to the body whose field within the heart is uniform will have a voltage produced in it proportional to the component of the heart vector in the direction of the field, regardless of irregularities in the shape and conductivity of the body and of dispersion of the electromotive forces of the heart.*

This fundamental principle is actually an immediate consequence of equation 9, but the above argument helps bring out its basic physical significance. In view of the irregular shape and conductivity of the body, it is of course by no means obvious that it is possible to find such uniform field or "heart vector" leads, and this is a question which has been investigated very carefully. These studies have shown that perfect leads of this sort can be constructed even when the outline and the variations in resistance of the body are taken into account, provided some simplifying assumptions are made concerning the latter. They will be described in the third paper of the series.

The Potential

The concept of the "indifferent electrode" also stems from the analysis of electric fields in the infinite homogeneous conductor. To understand how it can be applied to the body, despite the irregular shape and conductivity of the latter, it is first necessary to study the relation between the "potential" and the lead fields in an infinite homogeneous conductor.

The potential in such a conductor is defined as the voltage measured between the exploring electrode and a second electrode at infinity. At points remote from the heart this potential is proportional to the component of the dipole moment in the direction of the point, but this is not the case when the exploring electrode is near the heart. The reason for this is that the field of the lead formed by the exploring electrode and the electrode at infinity is then no longer uniform, but rather has the flow pattern of the type shown in figure 2*F*. The crowding together of the flow lines on the side of the "heart" toward the exploring electrode means that the lead field current is more intense there, and this in turn means that the voltage in the

lead is more sensitive to electromotive forces located there than to distant ones. Using the concept of the lead field, it is not difficult to derive an exact formula for the relation between the potential and these electromotive forces. It is

$$v = \vec{J} \cdot \vec{e} = (\vec{1}_r / 4\pi r^2) \cdot \vec{e} \qquad (13)$$

where $\vec{1}_r$ is a unit vector directed along the line going from the electromotive force to the exploring electrode. This formula states that the current density of the current flowing into the exploring electrode decreases inversely with the square of the distance from it, and is directed towards it. The factor 4π is necessary because the area of a sphere of radius 1 about the electrode is 4π.

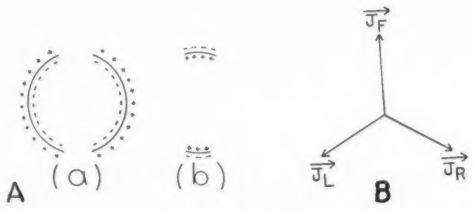

FIG. 3. See text

If the heart contains an electromotive surface which is almost closed, it is quite easy to locate the gaps in it by studying the potential about it. To see how this is done, consider the two distributions of electromotive force shown in figure 3*A*. The external voltages produced by these two distributions will be identical, because if the negative of one distribution is taken and added to the other, the result will be a closed surface having a uniform potential difference, and this will produce no voltage at all in any external lead, in accordance with a theorem previously proved. Thus, the small gaps in an almost closed electromotive surface will act like strong electromotive forces, and the surface itself will appear inert. This makes it easy to identify the gaps, and thus to identify infarcts, if they are the cause of the gaps.

It is not difficult to show with lead fields how the assumptions made by Einthoven justify the substitution of the central terminal for the electrode at infinity. He assumed that the heart and body are part of an infinite homogeneous conductor and that the three lead electrodes are situated in an equilateral triangle centered about the heart, which is supposed to be of negligible size in comparison with the dimensions of the triangle. In this idealized model, the current produced in the heart when the electrode at infinity is used can be thought of as the sum of two fields; the field of the exploring electrode as a sink, and the field of the electrode at infinity as a source. Since the latter is so far away, it produces no field in the heart, and the entire field is due to the current streaming into the exploring electrode. To show that the central terminal can be substituted for the electrode at infinity, then, it is necessary to show that equal amounts of current going into the three limb electrodes also produce no field at the center of the triangle. This is easily done. Since these electrodes are equidistant from the heart, and arranged in an equilateral triangle, the current fields they produce there will have the intensities and directions shown in figure 3*B*, and it is clear from the figure that the resultant of these three fields will be zero.

THE INDIFFERENT ELECTRODE

The idea of the potential may be applied to the body in the same way as was the concept of the dipole moment. The clinician would like to have the voltage measured between the "indifferent electrode" and the exploring electrode identical to the potential which would exist at the exploring electrode if the electromotive forces of the heart were in an infinite homogeneous conductor. That is to say, he would make the following definition: *an indifferent electrode is a reference electrode giving the same relative potential to the exploring electrode that it would have relative to infinity if it and the electromotive forces of the heart were part of an infinite homogeneous conductor.* Since the voltage will be the same only if the lead fields are the same, it follows that *an indifferent electrode is one which, together with the exploring electrode, produces a field within the heart which appears to radiate out from the exploring electrode in straight lines, and whose intensity there varies inversely*

with 4π times the square of the distance to the exploring electrode.

It is not difficult to construct an electrode of this sort. Various experiments have indicated that the central terminal is a good first approximation to one, provided that the exploring electrode is on the anterior chest. Methods of getting even better approximation are discussed in the third paper of this series. The possibility of perfect indifferent electrodes is also considered there.

It is important to realize that an indifferent electrode, as it is defined here, may be suitable for the exploring electrode at or near only one specific position. For example, although the central terminal seems to be a fairly satisfactory reference electrode when the exploring electrode is on the anterior chest, it is not when that electrode is on the back. It would be desirable to construct an electrode which would be indifferent regardless of the position of the exploring electrode, but this turns out to be completely impractical to do, even though it is theoretically possible.

Measuring the Accuracy of a Lead

The fields of practical leads never correspond exactly to the fields implicit in the idealized interpretations of them. The fields of heart vector leads, for example, are never precisely uniform, and the flow lines of indifferent electrode leads never precisely straight. In order to decide whether or not a lead is sufficiently accurate, it is desirable to have some quantitative index of its accuracy.

One way to do this is to compare the actual voltage produced in the lead with the voltage that would be produced in it if it were ideal. The actual voltage, v, will be in error by a certain percentage given in this particular case by

$$\epsilon = 100 \left| \frac{v - v_i}{v_i} \right| \qquad (14)$$

where v_i is the voltage that would be measured if the lead were ideal. It is natural to use a sort of average of this percentage as an index of the over-all error of the interpretation. The accuracy, α, of the lead can be conveniently defined as 100 less the percentage error; that is,

$$\alpha = 100 - \epsilon \qquad (15)$$

This accuracy will, of course, be dependent upon the location and the direction of the electromotive forces within the heart. For certain locations and directions of these, the accuracy may be zero; for others, 100 per cent. One can avoid having the concepts of error and accuracy of a lead dependent on the locations of the electromotive forces by supposing that the error and accuracy are defined for a random distribution of electromotive forces throughout the heart. This is a statistical concept which assumes that the electromotive forces are equally likely to occur at all points in the heart, and to have any direction.

To be specific, *the error, ϵ, of a given interpretation of a lead, in per cent, is defined as* 100 *times the ratio of the average magnitude** *of the error voltage, $v - v_i$, to the average magnitude of the desired voltage, v, when these voltages are produced by a set of random distributions of electromotive forces within the heart. The accuracy of the interpretation, α, is defined as* 100 *minus the percentage error.*

It is easy to express this definition in terms of lead fields. This is a consequence of the fact that a given lead field can be thought of as the sum of two fields; the ideal field and the error field, which must be added to it to yield the actual field. The ideal field and the electromotive forces will determine v and the error field and the electromotive forces, $v - v_i$. Since the average magnitude of the voltage produced by a random distribution of EMF's in any lead will be proportional to the average intensity of the lead field in the heart, it follows that equation 14 can be rewritten as

$$\epsilon = [\,|\,J_\epsilon\,|_{\text{Av.}}/|\,J_i\,|_{\text{Av.}}]100 \qquad (16)$$

where $|\,J_i\,|_{\text{Av.}}$ is the average intensity of the ideal field, and $|\,\vec{J}_\epsilon\,|_{\text{Av.}}$ is the average intensity of the error field which must be added to it to equal the actual field. That is, *the error ϵ of a given interpretation of a lead is* 100 *times the ratio of the average magnitude of the error field to the average magnitude of the ideal field, where*

* Since the electromotive forces are random, the same ratio would result if the root mean square values of the voltages were used, in place of the "average magnitude."

he error field is the field which must be added to he ideal field to equal the actual field.

As an example, let us consider the view, re-ently advanced by several authors,[6,7] that he voltages on the chest are, for all practical urposes, proportional to the projection of the eart vector on the lead. How accurate is this nterpretation of the chest leads?

To study this problem quantitatively we will eed a model of the body. For simplicity, let us hoose for this the infinite homogeneous con-uctor, assuming in addition that the heart is spherical in shape.

The mathematical procedure involved here (see Appendix for details) may be summarized as follows. The interpretation under consideration implies an ideal field in the heart which is uniform and parallel to the line joining the chest electrode to the center of the heart. The intensity of this ideal field is taken as equal to the vectorial average of the actual field, which for simplicity is calculated by assuming that the body is an infinite homogeneous conductor. The heart is assumed to be a sphere, and the second electrode of the lead is considered to be located at infinity. The average intensity of the error field, which is the difference between the actual and ideal fields, is then compared with the intensity of the ideal field, the exploring electrode being at a specified distance from the heart. The figure for the error of the interpretation, which results from taking the ratio of the average intensities of the error field and the ideal field, is then used to calculate the accuracy of the interpretation, using equations 15 and 16. This mathematical procedure leads to the graph of accuracy as a function of distance from the heart, shown in figure 4.

It is clear from this graph that the interpretation of chest leads in terms of the spatial vectorcardiogram is not likely to be very precise. The error ϵ here varies almost as a/R where a is the radius of the heart and R is the distance from the exploring electrode to its center. That is to say, when the exploring electrode is 2 heart diameters from the center of the heart, the error is about 25 per cent. When the distance is 1 diameter (half a diameter from the surface of the heart) the error is about 50 per cent.

Since the model of the body and the heart upon which this graph is based is obviously not an exact one, further studies of the same problem have been made using fluid mappers. In particular, the possibility that the high relative resistance of subcutaneous fat or the low relative resistance of the heart and blood would make the field substantially more uniform was investigated. These factors did tend to make the field slightly more uniform, but the change was by no means marked.

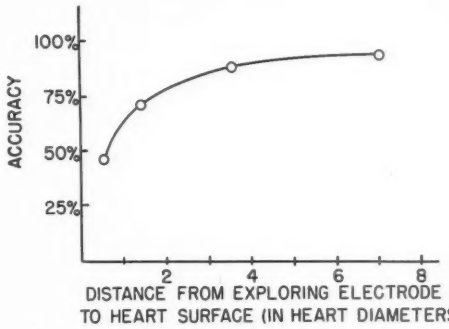

FIG. 4. Figure illustrating the accuracy of the assumption that the voltages in unipolar leads are proportional to the component of the heart vector in the direction of the exploring electrode. See text.

SUMMARY

This paper is the first of three which will deal with the study of electrocardiographic leads from the electrical point of view. The general purpose of this series is to discuss various experimental and theoretical technics which can be used in the analysis of a given lead and in the building up or "synthesis" of a lead having desired characteristics. The basic definitions and theorems which will be employed are developed in this first paper.

The most fundamental theorem relates the voltage produced in the lead to the electromotive forces of the heart by means of the "field" of the lead. The latter refers to the electric field set up in the body when a unit current is introduced into the lead. This theorem is closely related to the "lead vector" concept of Burger and van Milaan. It shows how the "dipole moment" and "potential" which would be associated with the electromotive forces of

the heart, if they were in an infinite homogeneous conductor, might be determined, despite the irregular shape of the body and the variation of the conductivity of its tissues.

In order to emphasize the relation of the idea of the lead field to previous studies of electrocardiographic leads, it is used in conjunction with Einthoven's assumptions to derive his triangle scheme, and to justify Wilson's substitution of the central terminal for the electrode at infinity. The Burger triangle is also discussed.

Because there will always be some difference between the interpretation of a clinical lead and its actual character, a quantitative method is developed for measuring the accuracy

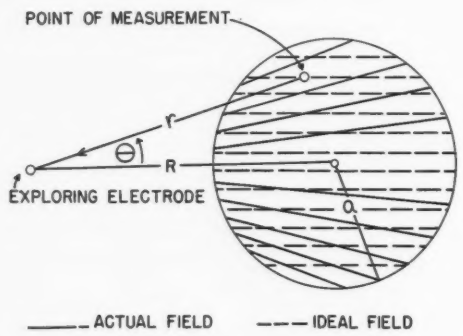

FIG. 5. See text (Appendix)

of such interpretations in terms of the fields of the leads. As an example, this method is used to test the view, recently advanced by several authors, that the voltages in the chest leads are due primarily to the component of the heart vector in the direction of the exploring electrode. It is shown that this view can be quite inaccurate when the electrode is close to the heart.

APPENDIX

The Accuracy of Considering the Voltages in Chest Leads Proportional to Components of the Heart Vector

The situation we are dealing with here, which involves approximations described in the text, is shown in figure 5. The solid lines in this figure are flow lines of the actual lead field, $\vec{J}$, and the dashed lines are lines of the ideal field, $\vec{J}_i$, which corresponds to the interpretation being investigated. The equation for the actual field in polar coordinates is

$$J = 1_r/4\pi r^2 \tag{1}$$

where $\vec{1}_r$ is a unit vector pointing towards the exploring electrode. The intensity of the ideal field is assumed equal to the vectorial average of the actual field within the heart. A theorem in potential theory* states that this average is equal to the intensity at the center of the sphere, thus

$$|\,(\vec{J}_i)_{Av}\,| = 1/4\pi R^2 \tag{2}$$

The components of this ideal field are given in polar coordinates by

$$\vec{J}_i = (\vec{1}_r \cos\theta/4\pi R^2) + (-\vec{1}_\theta \sin\theta/4\pi R^2) \tag{3}$$

where $\vec{1}_\theta$ is a unit vector perpendicular to the radius vector, which points in the direction of increasing θ.

The error field, $\vec{J}_\epsilon$, is given by

$$\vec{J}_\epsilon = \vec{J} - \vec{J}_i \tag{4}$$

Substituting equations 1 and 3 into this, we have

$$\vec{J}_\epsilon = \vec{1}_r\left(\frac{1}{4\pi r^2} - \frac{1}{4\pi R^2}\cos\theta\right) + \vec{1}_\theta\left(\frac{1}{4\pi R^2}\sin\theta\right) \tag{5}$$

The intensity of $\vec{J}_\epsilon$ at any point is equal to the square root of the sum of the squares of its components. That is

$$|\vec{J}_\epsilon| = +\sqrt{\left(\frac{1}{4\pi r^2} - \frac{1}{4\pi R^2}\cos\theta\right)^2 + \left(\frac{1}{4\pi R^2}\sin\theta\right)^2} \tag{6}$$

or, expanding

$$|\vec{J}_\epsilon| = \frac{1}{4\pi}\sqrt{\frac{1}{r^4} - \frac{2}{r^2R^2}\cos\theta + \frac{1}{R^4}} \tag{7}$$

The average value of $|\vec{J}_\epsilon|$ over the heart is given by the integral

$$|\vec{J}_\epsilon|_{Av} = \frac{1}{(4/3)\pi a^3}\int_{R-a}^{R+a}\int_0^{\theta_{max}} |J_\epsilon|\,(2\pi r\sin\theta)\,(r\,d\theta)\,dr \tag{8}$$

The factor $(4/3)\pi a^3$ represents the volume of the sphere.

θ_{max} here is given by the cosine law of oblique triangles

$$a^2 = r^2 + R^2 - 2rR\cos\theta_{max} \tag{9}$$

or

$$\cos\theta_{max} = \frac{1}{2rR}(r^2 + R^2 - a^2) \tag{10}$$

* See "Foundations of Potential Theory" by O. D. Kellogg, Berlin, Springer, 1929. P. 224.

It is convenient to change the variable of integration from θ to $u = \cos\theta$. This transforms equation 8 to

$$\vec{J}_\epsilon|_{Av} = -\frac{3}{8\pi a^3}\int_{R-a}^{R+a} r^2 \int_1^{(1/2rR)(r^2+R^2-a^2)} \cdot\sqrt{\frac{1}{r^4} - \frac{2}{r^2R^2}u + \frac{1}{R^4}}\, du\, dr \tag{11}$$

The first integration here is easily accomplished with tables of integration, and the result can be put in the following form:

$$|\vec{J}_\epsilon|_{Av} = \frac{1}{8\pi a^3}\int_{R-a}^{R+a} \frac{r}{R} \cdot\left[\left\{\frac{(R^2-r^2)}{R^2r^2} + \frac{a^2-(R-r)^2}{Rr}\right\}^{\frac{3}{2}} - \left\{\frac{R^2-r^2}{rR}\right\}^3\right] dr \tag{12}$$

Substituting for r the variable s defined by

$$s = 1 - \frac{r}{R} \tag{13}$$

equation 12 becomes

$$|\vec{J}_\epsilon|_{Av} = \frac{1}{4\pi R^2}\cdot\frac{1}{2}\int_{-k}^{k} \frac{s^3/k^3}{1-s^2} \cdot\left[\left\{(2-s)^2 + \left(\frac{k^2}{s^2}-1\right)(1-s)\right\}^{\frac{3}{2}} - \{2-s\}^3\right] ds \tag{14}$$

where k is a/R.

The authors have been unable to find a way to express this integral in elementary functions,* and for this reason have integrated it numerically, using the trapezoidal rule

$$\int_a^b f(s)\, ds \simeq h \cdot\left[\frac{f(a)}{2} + f(a+h) + f(a+2h) + \cdots + \frac{f(b)}{2}\right] \tag{15}$$

where h is the spacing of the intervals.

In evaluating equation 14 the value of the integrand was calculated at 20 points evenly spaced in the interval $-k$ to k for each specific R considered. (*R-2a, 4a, 8a* and *16a.*) The resulting four values for $|J_\epsilon|_{Av}$ are the basis of the four points of the graph shown in figure 4. A slide rule was used in these calculations, and as a result of its limited accuracy and approximations involved in numerical integration the graph in figure 4 may be in error by several per cent.

Sumario Español

Este trabajo es el primero de una serie de tres que tratará sobre la relación entre el voltaje de las derivaciones electrocardiográficas y las fuerzas electromotrices del corazón. El propósito general de esta serie es discutir varias técnicas experimentales y teoréticas que puedan ser usadas en el analisis de una derivación dada y en la construcción o síntesis de derivaciones de características deseadas. Los procedimientos usados son basados en un teorema fundamental que toma en consideración no tan solo la forma irregular y la conductividad del cuerpo pero si también la dispersión espacial de las fuerzas electromotrices dentro del corazón. Esto esta estrechamente relacionado al concepto de Burger y van Milaan de "vector de derivación."

En este primer trabajo las definiciones básicas y los teoremas se desarrollan. El segundo trabajo discute varios métodos de analizar las derivaciones. El tercero y último presenta un número de procedimientos sistemáticos para diseñar derivaciones vectorcardiográficas y unipolares. Estas derivaciones pueden tener exactitud substancialmente mas alta que las en presente uso, porque su diseño toma en consideración la forma y la conductividad del cuerpo y sus tejidos, y la localización excéntrica y extendida del corazón.

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* An approximate value can be found by using the variables

$$x = R - r\cos\theta; \qquad y = r\sin\theta$$

In this case equation 8 becomes

$$|\vec{J}_\epsilon|_{Av} \simeq \frac{1}{4\pi R^2}\cdot\frac{1}{(4/3)\pi a_2}\int_{-a}^{a}\int_0^{\sqrt{a^2-x^2}} \cdot\sqrt{4\left(\frac{x}{R}\right)^2 + \left(\frac{y}{R}\right)^2}\,(2\pi y)\, dy\, dx$$

And the exact solution of this is

$$|\vec{J}_\epsilon|_{Av} \simeq \frac{1}{4\pi R^2}\cdot 1.07\,\frac{a}{R}$$

That is

$$\epsilon = (100\,|\vec{J}_\epsilon|_{Av}/|\vec{J}_i|_{Av}) \simeq 107.\ a/R$$

This simple equation gives values which are very close to those found by numerical integration.

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The Kinetocardiogram

III. The Distribution of Forces Over the Anterior Chest

By E. E. Eddleman, Jr., M.D., and Kathryn Willis, M.D.

The distribution of the various motions of the anterior chest wall during the cardiac cycle has been studied, with particular reference to their magnitude in normal subjects. A few recordings of the posterior chest wall motions are included. Analysis of the type of distribution and localization of certain motions suggest their origin in terms of response of the chest wall to cardiac forces.

IN PRECEDING communications, a simple method of recording precordial movements was presented, as well as an analysis of the three types of patterns found in normal young adults.[1, 2] The present report presents an analysis of the distribution of various motions and magnitude of force over the entire anterior chest wall.

Method

The method of recording the movements over the chest, and estimating their magnitude, has been presented previously.[1] Records for this study were obtained from approximately 20 normal type I adult males. The amplitudes of the various movements have been estimated in 12 of these individuals. A few observations which have been made on both the anterior and posterior surfaces of the chest with the subject either lying on his right side or sitting. The motion of the posterior chest wall was studied in a few subjects, with the subject lying prone. Records were obtained from the right parasternal region in all intercostal spaces and designated as KV_1, first, second and third intercostal spaces, etc.: whereas tracings for the left parasternal space were designated as KV_2, first, second, third, fourth intercostal spaces, etc. The tracings from the left midclavicular line were designated as KV_4, first, second, third, fourth, and fifth intercostal spaces; while records from the midclavicular line on the right side of the chest were designated as KV_{3R} in the first, second, third, etc., intercostal spaces. Records obtained halfway between the left midclavicular line (KV_4) and the parasternal regions (KV_2) were designated as KV_3, second, third, etc., intercostal spaces; and the comparable portion of the right side of the chest were designated as KV_{3R}, first, second, third, etc., intercostal spaces. Records from the anterior axillary lines are designated KV_5 and KV_{5R}, with the intercostal space, and, similarly, the midaxillary line is designated as KV_6 (left chest) and KV_{6R} (right chest). Records were also obtained in the subclavicular region in the midclavicular line. All intercostal spaces were not explored in every subject; however, in the majority of subjects records were made from all areas.

Results

Patterns from the Right Side of the Chest. Figure 1 is presented to furnish a guide to nomenclature which has been previously discussed.[2] Figure 2 contains records obtained from KV_{3R} in the fifth intercostal space and in KV_{3R} in the second intercostal space. Note that the record lacks much of the detail of those obtained from the left anterior precordium. There are two significant features that should be pointed out: (1) There is a pronounced inward movement (I_2–E_1) immediately before and during the early part of rapid ejection (as determined by the carotid upstroke). (2) The outward movement during systole (E_1–E_2), which parallels the IJ upstroke of the displacement ballistocardiogram, is especially prominent. The peak of the movement (E_2) in records from the right upper chest usually precedes the J peak in the ballistocardiogram .01 to .02 second, while it usually follows the J peak in KV_{3R} records, and in records from the left upper chest. Most of the records from the right anterior chest are similar in this general type pattern. The initial inward motion associated with ejection (I_2–E_1), how-

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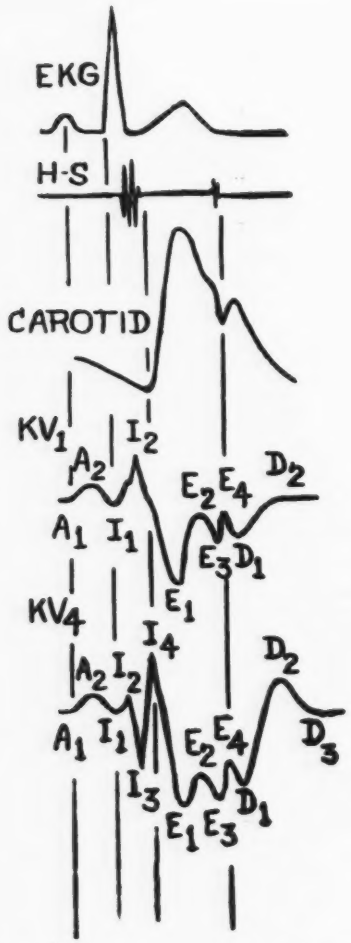

FIG. 1. The nomenclature for the kinetocardiograms is represented in a schematic drawing of records taken from KV_1 on the right side of the chest and KV_4 on the left side of the chest. The nomenclature is based upon a modified division of the cardiac cycle. All points between the onset of the P wave and the QRS complex in the electrocardiogram are assumed to be due to atrial contraction and the letter A is used to indicate the points occurring in this period. Although the isometric contraction phase technically begins with the onset of the first heart sound and ends with the beginning of ejection, the phase of protosystole as discussed in the preceding communication is included in this period. The motions which begin after the onset of the QRS complex in the electrocardiogram are presumed to be ventricular in origin since they occur in patients with auricular fibrillation and in complete heart block. The letter I is used to indicate this isometric contraction period. The letter E is used to indicate the period during ejection while the movements during diastole are indicated by the letter D. Note that the odd subscript numerals are all located in the valleys while the even subscript numerals are all located on the peaks of the various movements. Note also that the point I_2 in KV_1 on the right side of the chest occurs approximately at the same time as I_3 on the left side of the chest, since I_2 was the next definable point after I_1 on the right side of the chest. Thus the motion I_3 to I_4 is absent on the right side of the chest.

ever, is most pronounced in the region paralleling the lower portion of the sternum, and becomes much smaller in the upper chest, while the reverse is true with the outward motion (E_1–E_2) that parallels the IJ upstroke. (In figure 2 note that the diastolic movements are not prominent in any of these records obtained from the right side of the chest.)

Pattern of Records from the Left Anterior Side of the Chest. Figure 3 contains records from the left anterior chest at KV_3 in the third intercostal space. In contrast to the movements on the right side of the chest the outward systolic movement (E_1–E_2), which parallels the IJK wave in the ballistocardiograph, is small or absent. Conversely, the diastolic waves have become more prominent, especially the outward movement (D_1–D_2) which parallels the MN upstroke in the ballistocardiogram. The inward motion during early ejection (I_2–E_1 on the right and I_4–E_1 on the left) is similar in magnitude to that noted on the right chest, and is deepest in the lower parasternal area, and almost absent in the upper chest. Records from the lateral subclavicular area on both sides of the chest (fig. 4) resemble a mixed arterial and venous pulse tracing. It is probable that the pattern is, therefore, a transmitted pulse from the subclavian vessels. Thus records from the left chest have more prominent diastolic movements, while the records from the right chest have more prominent systolic movements.

Records Obtained with the Patient Lying on the Right Side and in the Sitting Positions. Although the records obtained with the patient lying on the right side are somewhat poor in quality, because the patient is usually unable to remain sufficiently quiet, there are several significant features. The anterior records with

patient lying on the right side are, in general, similar to the records obtained with the patient supine, although they are altered somewhat in amplitude. Motions of the posterior chest during protosystole and early isometric contraction, however, were opposite in direction to those obtained on the anterior chest (fig. 5). The records from the comparable positions from the back reveal that the inward motion associated with ejection (I_4–E_1) is similar to that noted over the anterior surface. The movement (E_1–E_2) which parallels the I-J wave of the ballistocardiograph is somewhat pronounced in records from the left posterior chest. The inward movement of the anterior surface of the chest during early isometric relaxation (E_4–D_1), followed by the outward movement (D_1–D_2), are noted on the posterior aspect of the chest to be in the opposite direction (fig. 5). In the sitting position, the record from KV_2 was identical to that obtained supine. The records directly opposite on the posterior chest revealed the same observations as obtained with the subject lying on the right side (fig. 6).

Records with the Patient Prone. A surprising finding was that with the patient prone, the records obtained from the posterior region in exactly the same position are completely altered from those of the posterior chest with the patient lying on the right side or sitting (fig. 5). The records resemble those made from the anterior chest in type II subjects. It is possible that the effect of gravity and the inability of the anterior chest wall to move with that posture produce the altered response, and the records become incomparable with the movements on the anterior surface of the chest supine.

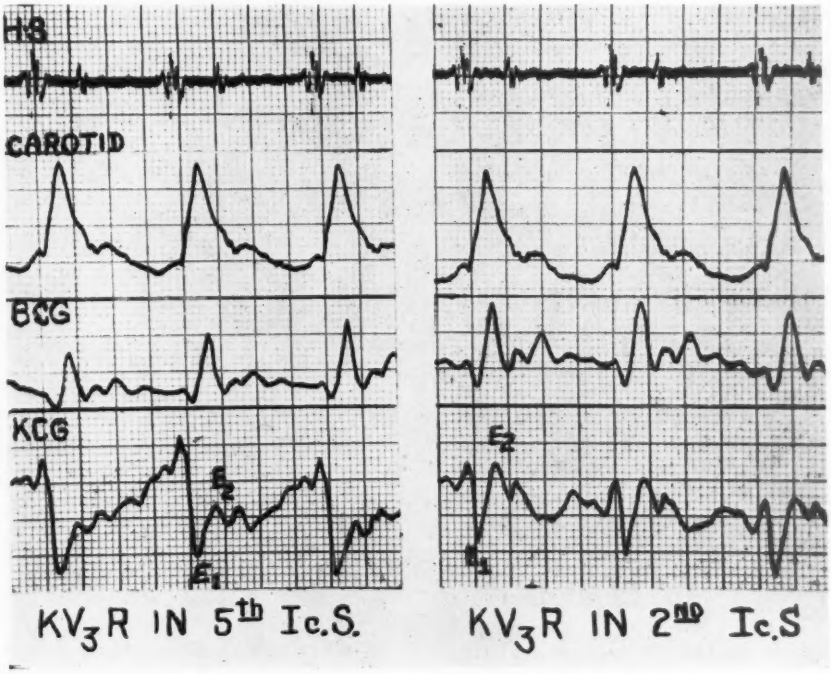

FIG. 2. Records from KV_3R in the fifth intercostal space and KV_3R in the second intercostal space. Note that the outward movement E_1-E_2, which parallels the IJ wave of the ballistocardiogram, is much more prominent in the upper right anterior chest wall than in the lower right chest. The inward motion, which begins just before carotid ejection, is more pronounced in the inferior region of the right anterior chest than in the upper portions of the anterior chest. In both records, the movements occurring during diastole are relatively small in amplitude.

Amplitude of Response. The most significant aspect of this study was the distribution of the forces in regard to the amplitude of the various movements. Figure 7 contains the mean amplitude of the outward motion (I_3–I_4) associated with the apical thrust, plotted in the various positions on the chest wall. Note that the force is maximal in the region of the point of maximal impulse and KV_3, and diminishes circumferentially in all directions, being absent over most of the right chest and on the upper left anterior chest. This movement is thus a localized movement to the region of the palpable apex thrust.

Figure 8 represents the mean amplitudes of the inward motion associated with ejection (I_4–E_1). Although the initial inward movement recorded from the right side of the chest is probably not related to ejection, the total inward movements, I_2–E_1 on the right and I_4–E_1 on the left, were measured. Note that the greatest magnitude of motion is noted in the lower parasternal area. This inward motion is symmetric in magnitude, being similar over the right and left chest, with a decrease in amplitude the further laterally the records are taken. Also, it is of note that this inward motion is very small or absent in the upper chest, and, occasionally, an outward motion may be detected.

Figure 9 is the representation of the mean amplitude of the wave (E_1–E_2) which parallels the IJ upstroke on the ballistocardiogram. The maximal amplitude is distributed over the right anterior chest, and extends down into the KV_{3R} and KV_{4R} areas in the fourth and fifth intercostal spaces. The area of maximal outward motion is noted in KV_{3R} in the second intercostal space (fig. 9). This outward motion E_1–E_2 is also fairly marked in the right parasternal area in the fourth, third, and second intercostal spaces. Only very small E_1–E_2 motions are noted over the left anterior chest and, when occurring, are of greater amplitude

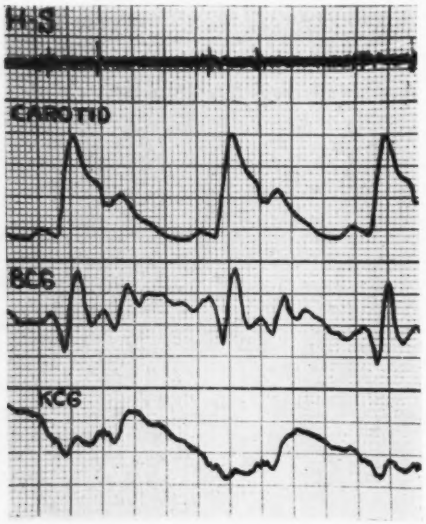

FIG. 3. Record obtained from KV_3 in the third intercostal space on the left chest. Note that the inward motions during ejection are small in amplitude, while the diastolic portions are much larger than those noted from the right side of the chest (fig. 2). It is important also that, in general, the detail or records from the upper left chest are somewhat poor in quality.

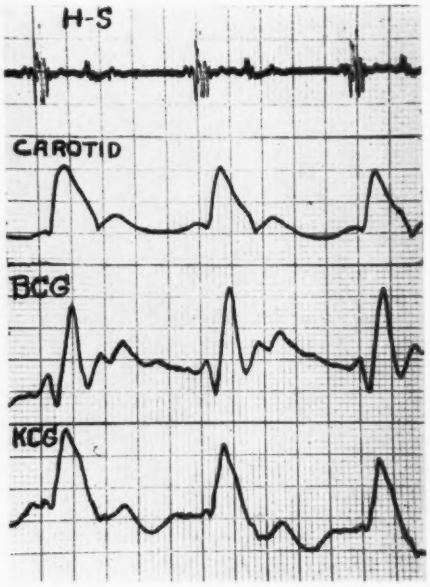

FIG. 4. Record obtained from the infraclavicular area. Note the marked resemblance of this record to a carotojugular type of pulse tracing. It is probable that this represents a mixed arterial venous pulse tracing transmitted from the subclavian or axillary vessels.

in the upper portion of the chest in the region of the second intercostal space. The outward motion (E_3–E_4), which begins with or just before the phase of protodiastole, is equally distributed over the lower left and right chest

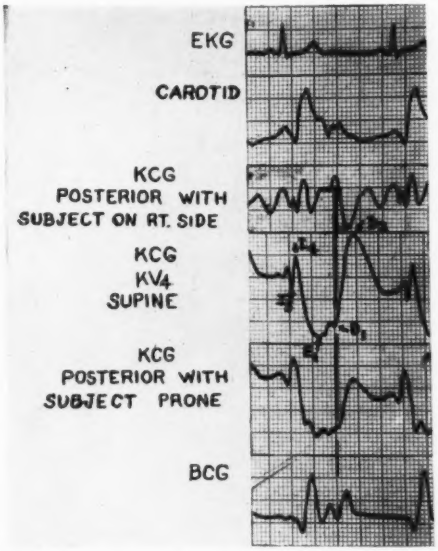

FIG. 5. Composite figure of records obtained in the KV_4 position with the subject supine, from the posterior aspect of the left chest with the subject lying on the right side, and from the posterior aspect of the left chest with the subject prone. It was possible to superimpose these records, since they were of approximately the same cycle length. The movements from the posterior chest (with the patient lying on the right side), which occur during the isometric contraction period and the isometric diastolic period, were of opposite directions to the movements from the anterior chest (supine). Note that the record from approximately the same position on the posterior aspect of the chest is entirely changed when the patient is prone. However, the movements during the isometric contraction period are still opposite in direction to those noted on the anterior surface, while the marked outward movement (D_1-D_2) in diastole is now in the same direction as that obtained supine.

in the parasternal regions, as is the distribution of the inward movement (E_4–D_1) that parallels the LM downstroke of the ballistocardiogram (fig. 10).

The outward motion (D_1–D_2) which parallels the MN upstroke in the ballistocardiogram, and which occurs during the phase of isometric relaxation, is most prominent in the left lower parasternal region (fig. 11). This motion is somewhat localized, with an average amplitude of approximately 50 to 70 microns in the left parasternal region, falling off fairly rapidly to 25 microns in KV_1 and around 19 microns in KV_5. Although D_1–D_2 is present both in the right chest and in the left chest, the localiza-

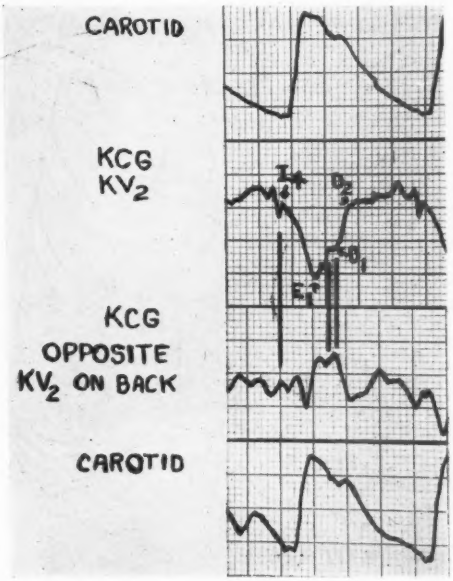

FIG. 6. Record of the anterior KV_2 and opposite position, posteriorly, obtained from a subject in the sitting position. Note again, as in figure 5, that the movements on the posterior aspect of the chest are, in general, opposite in direction to those on the anterior side. It is important that the movement (D_1-D_2) beginning in isometric diastole is opposite in direction on the posterior side to that on the anterior side, suggesting that at this time the entire heart is moving anteriorly, pulling the posterior aspect of the chest inward.

tion of the marked outward movement over the main mass of the ventricular muscles suggests that this motion is an impact phenomenon like that of the apex beat, but probably produced by the entire heart pounding against the anterior chest wall.

DISCUSSION

The distribution of the various movements studied gives some evidence of the underlying

mechanisms involved. Thus a movement localized over the heart suggests that the impact of the heart on the chest wall is responsible. A bilateral distribution of a movement suggests other factors are involved, rather than the local action of the heart. Therefore, the movements can be divided into several categories.

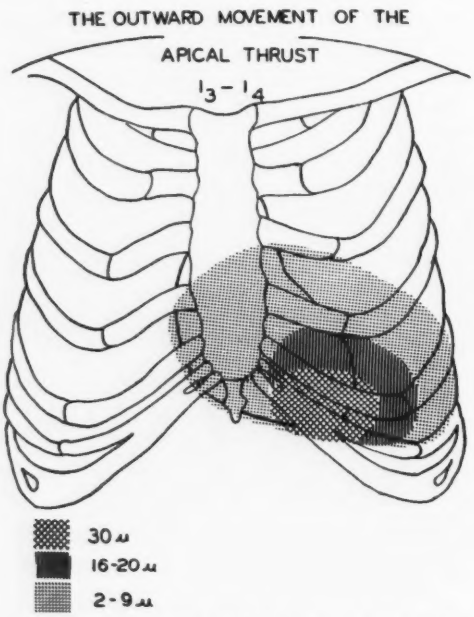

FIG. 7. Diagram of the distribution of the magnitude of the force I_3-I_4 (the apical thrust) over the anterior chest. Note that the outward movement is greatest in amplitude over the apical region of the heart, diminishing circumferentially in all directions and being almost absent over the right anterior chest. The localization of this movement to the region of the apex offers evidence that the outward movement (I_3-I_4) is produced by the thrusting or the impact of the apex against the anterior chest wall.

The amplitude of some of the smaller movements, especially those occurring during protosystolic and early isometric contraction (I_1–I_2)(I_2–I_3), were not measured and, therefore, the distribution of magnitude will not be discussed.

Movements as the Result of the Impact of the Heart on the Chest Wall. The marked localization of the outward movement just preceding ejection (I_3–I_4) (fig. 7) suggests that this is produced by the impact of the apex against the chest wall. Evidence will be presented later that this is probably the result of the heart rotating to the right, thrusting the apex outward and producing the apex beat. Clinically, this is the movement correlated with the apical thrust, and is larger in magnitude in those subjects with an easily palpable apex beat.

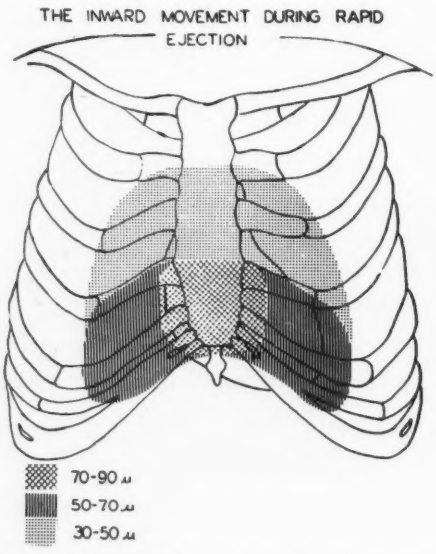

FIG. 8. Magnitude of the inward motion during rapid ejection (I_4-E_1 on the left chest and I_2-E_1 on the right chest) is represented. Note that the area of maximal inward motion occurs in the lower parasternal regions, diminishing on both sides and in the upper anterior chest. There is a small inward motion occurring elsewhere over the chest below 30 microns in magnitude. It is important to point out that this motion is bilaterally symmetric in magnitude, although the inward motion begins slightly earlier on the right side of the chest than that on the left chest. The symmetric aspects of this motion suggest that this is possibly the result of: (1) change in intrathoracic pressure as a result of a shift of blood with ejection; (2) a shift of blood from the lower to the upper aspects of the chest; (3) the movement of the entire heart, posteriorly, pulling inward the anterior surface of the chest.

Similarly, the localization of the outward movement beginning during isometric relaxation (D_1–D_2) (fig. 11) suggests that this is the result of an impact. However, the wider distribution over the main cardiac mass, suggests

the entire heart is striking the anterior chest wall. The occurrence of the inward movement, as recorded from the posterior chest wall (fig. 6), simultaneous with the D_1–D_2 outward movement from anterior chest wall, also adds

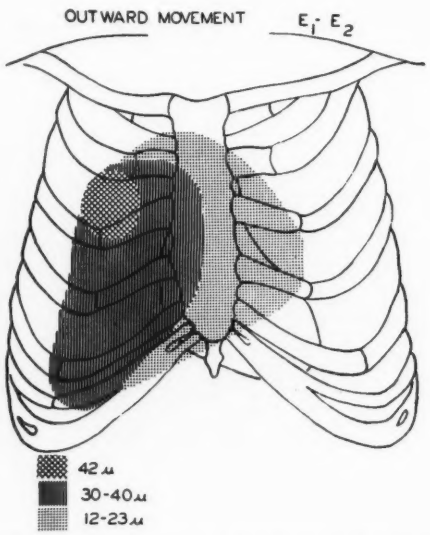

FIG. 9. Diagram of the distribution of the magnitudes of the outward movement E_1-E_2, which parallels the IJ upstroke of the ballistocardiogram. Note that the greatest magnitude is located in the upper right chest, or in the anatomic direction of the ascending aorta. The localization of the greatest magnitude of this movement to the upper right chest suggests that it is the result of the impact of blood in the aorta. The movement does occur over the left anterior chest but is of small magnitude, being most pronounced in the upper left chest. However, in most individuals this movement usually is absent in the left anterior chest. The distribution of the force to the right lower aspect of the chest is possibly the result of a transmission of the outward movement to the more movable portions of the chest wall or to impacts of blood in the pulmonary artery, while it is modified by the presence of the heart on the left side of the chest.

evidence that this is an impact of the heart on the anterior chest wall.

The occurrence of such a pronounced movement, associated with the relaxation process, is of note. The force producing this movement is apparently directed anteriorly and slightly to the left. In one subject the upper lateral aspect of the right chest moved inward, associated with the large leftward and outward movement over the left precordium.

Movement as the Result of Shift of Blood Volume. The distribution of the inward movement with ejection (fig. 8) suggests that the principal force moving the chest inward is symmetrically distributed, affecting the right as well as the left side of the chest. Anatomically, the lower sternal area is the most movable, being farthest from the relatively

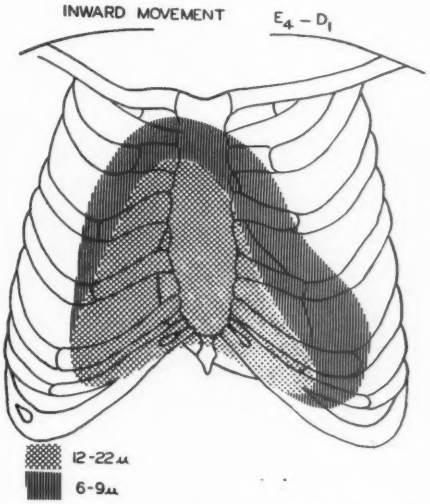

FIG. 10. The inward motion E_4-D_1 is of small magnitude on all portions of the anterior chest; however, the general distribution is somewhat symmetric in character. This suggests that the heart at this time is moving posteriorly in the chest cavity, pulling the anterior chest wall inward.

more fixed portions of the chest wall (the spine and the clavicular area). It appears that the inward movement (fig. 8) is maximal in the areas of the chest which are more movable. This generalized type of motion is possibly produced by a decrease in pressure in the thoracic cavity as the result of a decrease in the intrathoracic blood volume associated with the ejection process, or a local shift of blood from the lower aspect of the chest to the superior part. An additional possibility is simply that the entire heart is moving posteriorly.

The fact that the right chest begins moving

inward before the left chest, or about the time of the outward movement (I_3–I_4) of the apical thrust, suggests additional factors initiating the inward movement.

Movements Due to Impact of Blood on the Great Vessels. The outward movement (E_1–E_2) which parallels the IJ upstroke of the ballistocardiogram was distributed largely to the right anterior chest (fig. 9). The fact that this motion is synchronous with or may precede the J peak by 0.01 to 0.02 second, is evidence that the two movements are related. If impacts of the blood in the aorta produce the IJ upstroke, as has been demonstrated by Starr and co-workers,[3] then the E_1–E_2 should be directed upward anteriorly and to the right in line with the anatomic path of the great vessels. From figure 9 the force is maximal in the upper right chest, which is consistent with this hypothesis. The force is also distributed to the right lower lateral aspect of the chest and probably represents the impacts on the pulmonary arteries or merely a transmitted movement. The chest, as has been pointed out, is more movable in the lower aspect and, therefore, E_1–E_2 in KV_{3R} and KV_{4R} in the fourth and fifth intercostal spaces would be expected to be of fair magnitude.

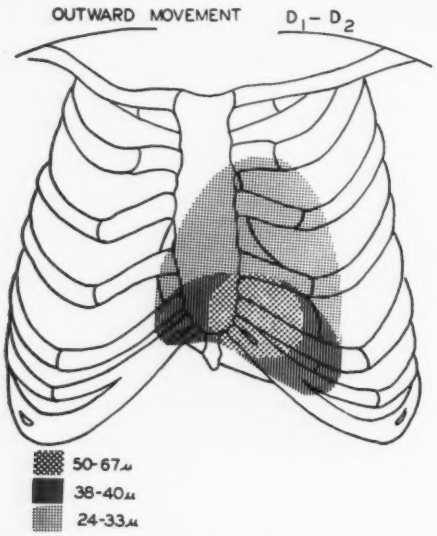

FIG. 11. Diagram of the distribution of the amplitude of the outward movement D_1-D_2. The greatest amplitude is located just to the left of the sternum over the main myocardial mass. The motion also occurs elsewhere over the anterior chest. However, it is of small magnitude (below 24 microns). The localization of the greatest magnitude of this force to the left parasternal region suggests that this movement is the result of an impact of the heart against the anterior chest wall.

The almost complete absence of the movement (E_1–E_2) in the left chest is probably the result of local cardiac forces nullifying the impact phenomena. The distribution of forces upward and slightly to the right is, however, somewhat at variance with the spacial vector of the IJK wave, as determined by a rotating ballistocardiograph table. Scarborough and co-workers found the vector of the IJK wave to point to the left and slightly posteriorly.[4] It is possible that as the force actually begins, it points anteriorly and to the right, then rotates to the left and posteriorly. This would be additional evidence of why there is an apparent absence of this movement over the left anterior chest, and why the movement is more pronounced over the posterior aspect of the chest.

CONCLUSIONS

1. A study of the distribution of forces over the chest wall has been made in normal healthy young adults.

2. The motion associated with the apical thrust (I_3–I_4) has a localized distribution of magnitude.

3. The inward motion (I_4–E_1) associated with ejection is maximal in the lower parasternal region, diminishing peripherally, and is symmetric on both right and left sides of the chest.

4. The outward movement (E_1–E_2) that parallels the IJ upstroke in the ballistocardiogram is maximal in the right upper chest, being almost absent over the left anterior chest.

5. The outward movement (D_1–D_2) that parallels the MN upstroke on the ballistocardiogram is directed anteriorly and slightly to the left, and is centered over the cardiac area.

Sumario Español

Se ha estudiado los varios movimientos de la pared torácica anterior durante el ciclo cardíaco, con particular interés en su magnitud en sujetos normales. Algunos trazados de los movimientos de la pared posterior se incluyen. Análisis del tipo de distribución y localización de ciertos movimientos sugiere su origen en términos de respuesta de la pared torácica a las fuerzas cardíacas.

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A Method of Securing the Direct Body Ballistocardiogram by Means of a Microscope, Giving a Record Readily Calibrated

By E. W. Bixby, M.D., and C. B. Henderson, M.D.

We describe a simple method of recording the direct body ballistocardiogram by means of a microscope and a powerful light source. The beam passes through a slit attached to the body, and the image of this moving slit is magnified by the microscope and focused on moving photographic paper. When a static force is applied to the body, the base line of the record is permanently displaced and so the amplitude of the ballistocardiogram can be calibrated. By superimposing a ballistocardiogram obtained by means of the electrocardiogram on the same film, accurate comparisons of the two records and a calibration of the electrical instrument can be obtained.

BALLISTOCARDIOGRAPHS of the portable or direct body type were first designed by Dock and Taubman.[1] Several types of these instruments now exist; they all record the motion of a bar placed on the shins of a subject lying on a rigid surface, by one of the several kinds of simple electrical pick-up units, and all use a standard form of electrocardiograph for recording the record. In these instruments the saving of expense over the table type of apparatus has been very great and, available commercially in several types, they are now widely used. Unhappily, unlike the table types of ballistocardiographs,[2,3] a calibration of the static type cannot be applied to records secured from these portable instruments, for when a constantly acting deflecting force is applied to the body, because of the nature of the electrical circuits, the base line of the record returns to the original base line immediately. To meet this situation, attempts have been made to calibrate by means of a blow of short duration, but this method has been found unsatisfactory. Exact duplication of results is difficult, probably for several reasons. The spike produced on the record from a blow does not arise from the base line but is superimposed on that part of the subject's ballistocardiogram that is taking place at that instant, and the correction for this is not readily applied. Also some subjects cannot avoid tensing muscles in anticipation of the blow and this affects the tracing recorded. So the majority of doctors employing portable ballistocardiographs have proceeded with their clinical work without attempting to calibrate their records at all. Needless to say, the shift of the record caused by the introduction of the 1 mv. does not standardize ballistocardiograms recording through electrocardiographic equipment, although it is necessary to standardize the amplification introduced by the electrical apparatus itself.

Ballistocardiograms can become abnormal in three ways: because they are abnormally large; because they are abnormally small; or because the contour of the record is abnormal. Without a method of calibrating for sensitivity the operator is limited to detecting gross abnormalities of the last type. This is an important field, but certainly the utility of the simple portable ballistocardiographs would be greatly enhanced by devising a type of apparatus which could be easily calibrated, and which would thus permit a quantitative approach to many fundamental problems which cannot be attacked effectively from a purely descriptive viewpoint.

In this communication we will describe a

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type of portable apparatus so simple that it can be constructed of parts already available in all hospitals and to many doctors, and so at little or no expense. And, as our preliminary report indicates,[4] it can be readily calibrated for sensitivity by the same static method now in use for the table types. No attempt will be made at this time to present abnormal records, or to discuss the more complex theoretic problems; we shall content ourselves with a detailed description of the method, its calibration and other advantages. Publication is made at this stage of the work because the opportunity for further collaboration has been denied us.

Apparatus

We first set up the method[4] with a light beam system and photokymograph which had been gathered together for another investigation, but we soon found that equally good records could be secured by using equipment available in most hospitals and to many doctors, so only the latter will be described. One needs:

1. A compound microscope of any standard type. It is convenient to have one with a hinge above the stand, which permits the barrel to be placed in the horizontal position. The lower power, a lens of 10 mm., was used with oculars of 10, 15 or 25 power, the choice depending on the distance from ocular to camera.

2. A light source with a powerful bulb. We have been using a 200 watt General Electric precision lamp for optical devices in a Bausch and Lomb lamp housing type 31-33-75. This housing was supplied with a diaphragm and a lens.

3. A standard electrocardiograph with a photographic recording camera. We have secured good records with both Cambridge and Sanborn types. When using a Sanborn electrocardiograph the wooden case had to be removed to admit the beam and to mount the mirror, but when using the Cambridge instrument this was not necessary.

4. A mirror for deflecting the beam into the camera. We used a front surface mirror made on a piece of plate glass by the Evaporated Metal Film Co. of Ithaca, New York, but a back surface mirror could be used with but little loss. This mirror was mounted on a brass support attached to the frame of the electrocardiograph so that the beam was turned into the camera without parallax to the beam of the electrocardiograph.

5. A light beam slit. This we made ourselves from a strip of brass plate perforated by a long slit. The upper part of this slit was used to bolt the plate at right angles to the end of the shin bar. The lower part of the slit

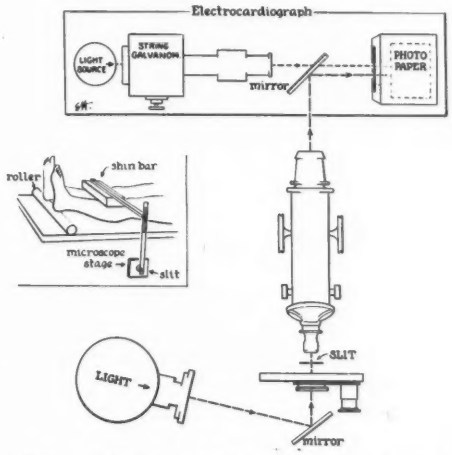

Fig. 1. Diagram of the setup for obtaining a ballistocardiogram from the shins of the subject by means of a microscope, using a standard form of electrocardiograph as the recording device. In the instance shown a Cambridge electrocardiograph was used.

was narrowed by two razor blades cemented to the brass edge and adjusted to give a slit of satisfactory width through which the beam was passed. In place of the slit it has recently been found convenient to use a glass slide ruled with parallel black lines 60 to the inch and sold under the name of Ronchi rulings by the Edmund Scientific Corp. of Barrington, N. J. The multiple lines can be focused satisfactorily, the image appearing as alternating light bands and dark shadows with a similar ballistocardiogram on every edge. Before one record goes off the film another appears from the opposite side, so it is never necessary to center the slit.

6. A well made pulley, which could be clamped to an upright iron rod at any desired height, the rod being clamped in turn to the table edge; a strap to go around the ankles; a cord; a set of weights and a pan to hold them. These were required for the calibration.

7. A bar to be placed across the shins of the subject.

To set up the apparatus as shown in figure 1, after the microscope's condenser had been removed, the various parts were adjusted until a bright beam was centered on the camera aperture. The diaphragms, both in the lamp and in the microscope, were narrowed to cut out extraneous light until they began to diminish the intensity of the beam. Then, all

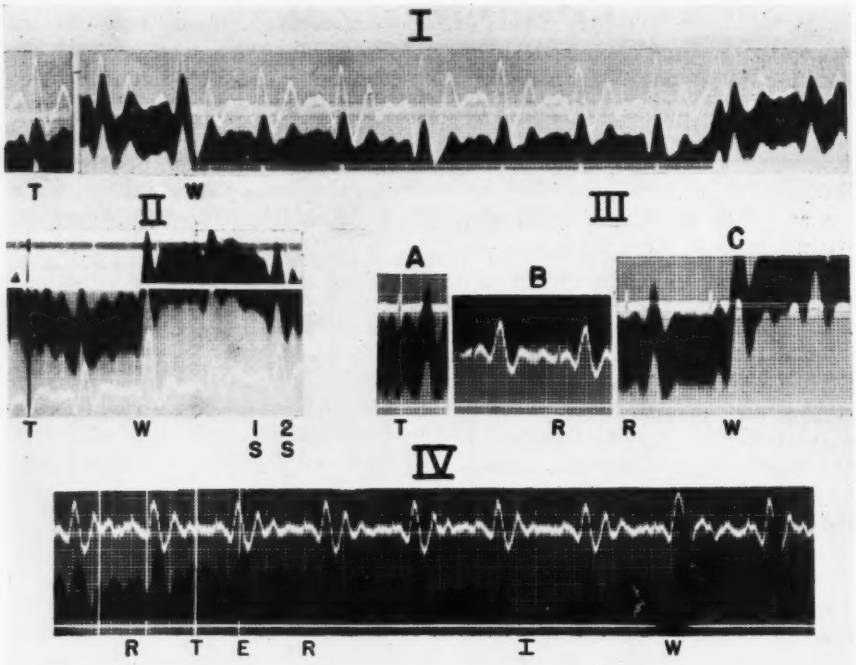

FIG. 2. Tracing secured by the microscope ballistocardiograph, compared with the electrocardiogram, heart sounds, and with records from several types of electrical ballistocardiographs. "T" indicates a test for alignment; at "W" the calibrating weight of 300 Gm. was applied or lifted off. "R" indicates the position of the electrocardiograph R wave. Time is indicated by the vertical lines; the smallest interval is 0.04 second.

I. The tracing of the microscope method is on each edge of the heavy black line. The moving white line is the ballistocardiogram taken by the Sanborn photoelectric instrument. The horizontal white line is an artifact which appears when one form of Sanborn electrocardiograph is used as recording apparatus. Note the base line shift in the microscope record, and its absence in the electrical record when the calibrating weight is applied and removed in this and the later records.

II. The tracing of the microscope method with a simultaneous record of heart sounds, both taken by a Sanborn electrocardiograph equipped for sound recording. "1S" and "2S" are placed under the corresponding sounds of the last systole shown.

III. (*A*) The tracing of the microscope method with the electrocardiogram. (*B*) The tracing of the microscope method superimposed on the ballistocardiogram taken from an electromagnetic ballistocardiograph of the type introduced by Dock.[1] The electrocardiogram has been thrown into the latter record causing the "pip" seen over the letter "R." (*C*) The tracing of the microscope method with an electrocardiogram both taken through a Cambridge electrocardiograph.

IV. Comparison of microscope record with a velocity tracing obtained by a coil and magnet method (white line), R, T and W as above; at E expiration begins, at I inspiration begins.

being in adjustment, the lamp, microscope and electrocardiograph were tightly clamped to a wooden board so that they could be moved as a unit without disturbing the adjustment.

Securing the Record

The subject lay on a strong laboratory bench and the apparatus was placed on a table beside. A roller was placed under his heels. The shin bar was placed across his shins at a distance from the heels varying from 15 to 35 cm., and the slit was adjusted to lie just beyond the stage of the microscope. The image of the moving edge was focused on the camera aperture by the coarse and fine adjustments of the microscope and the record was taken.

Reading the Record

Typical records are shown in figure 2. Identical ballistocardiograms are written by both sides of the slit and either can be used. Because the respiratory weaving sometimes throws the beam off the film, we found it advantageous to use a wide slit. When the edges were kept several centimeters apart on the record the danger of both going off the film was greatly reduced. Eventually the substitution of the Ronchi rulings eliminated this problem.

The individual waves can be readily recognized and, if this proves difficult, a simultaneous electrocardiogram can be taken to aid in their identification; for the recording of the ballistocardiogram through the electrocardiograph's camera in no way interferes with the taking of an electrocardiogram in the usual manner through the same instrument.

Calibration

The pulley was firmly attached to the upright iron rod clamped to the footward edge of the table. The calibrating weight was suspended by a string which, after traveling over this pulley, was tied to a strap placed firmly around the ankles of the subject. The height of the pulley was adjusted so that the course of the string from pulley to subject was horizontal and parallel with the long axis of the body. To calibrate the record the weight was either lifted off and reapplied, or applied and then lifted off, while the record was running.

Calculating the calibration from the record was not as easy as in records secured by table ballistocardiographs because respiratory arching is always present unless the breath is held, and in some subjects it is of considerable magnitude; therefore, during breathing the base line is never straight. But in quiet breathing it is not hard to estimate the deflection with an accuracy sufficient for most types of clinical work and, if necessary, accuracy can be further

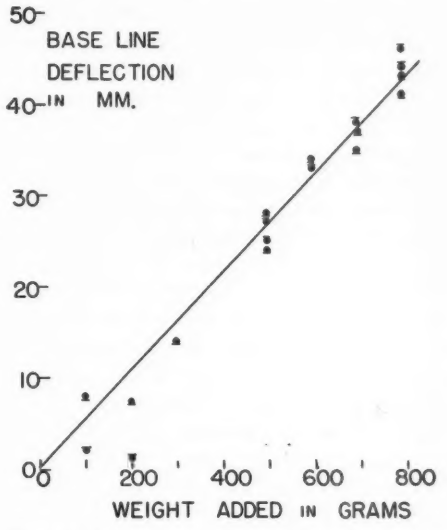

Fig. 3. Calibrations of the microscope ballistocardiogram, displacement of the record base line caused by the application of graded forces to a single subject.

improved by calibrating while the patient stops breathing. But in either event, no calibration should be accepted unless the base line returns to its original position after the distorting change of force has been removed. This precaution provides a safeguard from errors due to slipping of the subject along the table, failure to hold the breath steady and the like.

Figure 3 shows repeated calibration with different weights on one of our subjects which is typical of many such estimations made while the subject was breathing normally. Obviously, when heavier weights are employed

the deflection is larger and the effect of the error of reading the base line on the estimate is correspondingly diminished. But weights causing deflections larger than the ballistocardiogram could be properly used to calibrate the latter only if the calibration were linear. The data in figure 3 support the belief that the body's spring has a linear calibration over the range in which we are interested, although our accuracy and the number of cases studied is probably not yet great enough to rule out a small curvature. The scatter of the data in figure 3 permit a judgment of the accuracy we were able to secure in a blind test as the records were read without knowledge of how much weight had been applied. When the weight applied was 200 Gm. or under, the error of reading the base line usually prevents a satisfactory calibration. When weights of over 1 Kg. were applied large artefacts often appeared, sometimes obviously due to slipping of the subject on the table, but at other times perhaps due to changes in the characteristics of the body's spring. Weights of from 300 to 500 Gm. proved most satisfactory; it would appear that one point is all that need be established and that the line joining this point with the origin will define the relation of any ballistic amplitude to force with an accuracy sufficient for most clinical work.

Discussion

Good examples of the types of records secured are given in the figures. Unlike records obtained with the resisted table types of apparatus, respiratory weaving of the base line is a prominent feature of all records made during normal breathing. While this makes the base line harder to identify, it has certain advantages; the amplitude of the systolic complexes varies with their position in the respiratory cycle, as is well known. Any variation from the usual pattern could be detected in most ballistic records only by taking a simultaneous record of respiration. But in our record, the position of each systolic complex in the respiratory cycle can be seen at a glance.

While the general character of the cardiac waves resembles closely that recorded by resisted tables there are noteworthy differences. The waves tend to be a little broader in time, as are those recorded by the Nickerson[3] type of table ballistocardiograph. This seems natural enough because of the restoring force of the body's spring, as the steel spring in Nickerson's instrument, is much weaker than the heavy spring used in the resisted table types. The magnification in the original table used by Starr and his associates, the instrument used for these comparisons, is about 500 times; the magnification of our direct photographic instrument need be only about 250 times to secure records of approximately similar size, so the actual body movement recorded is much larger in the conditions under which our instrument is used.

Our experience with the use of the microscope method to calibrate electrical methods will be briefly described. The slit of the microscope method was attached to the same shin bar which carried the light source or pick up unit of the electrical instrument. The ballistocardiograms of both instruments were recorded on the same film and, after alignment, one was adjusted until the records were identical in size. Then the calibration of the microscope method can be applied to the record of the electrical instrument. Thus a magnification of 177× by the microscope produced a record identical with that of our Sanborn photoelectric ballistocardiograph when the electrocardiograph was standardized so that 1 mv. displaced the base line 15 mm.; a magnification of 118× by microscope equalled a standardization of 1 mv. = 10 mm.

A magnification of 245× is about the upper limit of our present microscope ballistocardiograph. This gives a record much similar in size to that of the ballistic table used in this laboratory. Higher magnification would require more light than our present source provides and it becomes more difficult to maintain focus. A great many of our records were taken with a magnification of 177× and this was very satisfactory.

In a study of the relationship between corresponding wave areas of the two records, cardiac output was estimated by Tanner's formula[5] 12 times on 10 subjects; first from

records secured on the rigid table by the microscope method and then from records secured on subjects lying at rest on the resisted moving table. The cardiac output estimated from the former records was calculated to average 80 per cent of the value estimated from records secured on Starr's table. We conclude, therefore, that in the records of the direct photographic instrument the I and J waves are not only somewhat broader in time but also of less amplitude and of a little smaller area than similar waves recorded by resisted table instruments. Because the body's spring is weaker than the strong steel spring of the resisted table, the record of the microscope method is less highly differentiated, and for this same reason respiratory weaving of the base line appears in one and not in the other.

It should be pointed out finally that contour of the waves in the direct photographic record is very similar to that secured on Starr's resisted table when the subject's heels are not in firm contact with the footplate.

The relation of our records to those secured from three types of portable electrical instruments can be summed up by the statement that they are practically identical. Examples of simultaneous recordings secured from several types of these instruments are given in figure 2. The manufacturers are to be congratulated, for had there been a discrepancy there is no doubt where the truth would lie; the microscope has the last word in the estimation of small movements. It is also to be noted that in the electrical instruments, when respiratory weaving has been taken out by electrical means, this has been accomplished without noteworthy damage to the recording of the cardiac complexes. But we are by no means confident that every one of the multiplicity of electrical devices now made and sold for recording the ballistocardiogram would pass the test so well, and we believe that the direct microscopic method will be useful in estimating the degree of distortion produced when new devices are introduced.

Despite this agreement in contour between records of the movement recorded through the microscope and those picked up and amplified electrically, when the calibrating weight is applied to the body the two records behave very differently. The base line of the microscope record is deflected at once, and it remains at its new level as long as the force is applied. In records from the electrical devices, however, if the weight is applied or lifted off suddenly a spike is seen, but if the distorting force is applied gradually the record is affected little if at all.

The microscope method can be used to calibrate the electrical methods indirectly. Thus in any subject, after ascertaining the amplitude of the record obtained through the microscope, in terms of force, by our method of calibration, one can adjust the amplitude of the electrical method to the same value. It is also planned to investigate how closely the strength of the body's spring can be related to body size and build; if this relation is found to be consistent, a table of the values found would help one predict the normal values in records difficult or impossible to calibrate accurately at every run.

Our experience in taking records from a bar laid across the shins both with and without being fastened to them has disclosed a difficulty which we believe has not been previously emphasized enough. The exact position of the bar on the shins may make considerable difference in the amplitude and form of the record. We have demonstrated in a number of our subjects that the amplitude of the tracing increases as the shin bar is moved from just above the ankles towards the knee; in some subjects the difference is large. Changes in the contour of the diastolic waves may also appear. We have not as yet investigated the cause of these differences, but we believe that, as direct body ballistocardiographs become more quantitative, knowledge of such inconsistencies will become increasingly important.

Finally it should be pointed out that by means of a pointer attached to the shin bar and brought into focus over the stage of any microscope, the ballistocardiogram can be directly viewed by any doctor. By our technic the record can be focused on any screen, wall or ceiling. Unfortunately, the movements are too quick for the eye to appreciate in detail; one cannot separate with confidence one wave

from another of similar direction; and so one cannot distinguish the characteristics of single waves. But the over-all amplitude can be readily seen and, indeed, roughly measured by an ocular micrometer if viewed through the microscope, by a ruler if thrown against the wall. The respiratory variation is also seen clearly, and the extent of base line shift caused by the application of the calibrating weight is readily ascertained. A crude test of this kind leaves much to be desired, but it is within the reach of every doctor practicing medicine, and it might well provide better evidence of the forcefulness of cardiac action than does any part of the routine history or physical examination in use today.

Summary

1. A simple form of ballistocardiograph is described in which the movement of a bar across the shins is magnified by a microscope and recorded in the camera of a standard electrocardiograph.

2. This method gives an accurate record of displacement and it can be calibrated readily by applying a known force to the patient's body which causes a permanent displacement of the base line of the record.

3. Examples of tracings secured by the microscope method are shown. Simultaneous tracings secured by several types of electrical methods were almost identical, but electrical records cannot be so calibrated because the application of a static force to the subject does not cause a permanent displacement of the base line of the electrical records.

Acknowledgments

The authors wish to express their sincere gratitude to Dr. Isaac Starr for the basic idea which led to this work and for his stimulation, great interest, and valuable assistance in both preparing the experiments and presenting the material.

The authors also wish to thank many confreres for their cooperation in consenting to be subjects; particularly Mrs. Ruth Besser and Mrs. June Silverman.

Sumario Español

Describimos un método sencillo de registrar el balistocardiograma de cuerpo directo por medio de un microscopio y una fuente de luz fuerte. El rayo pasa através de una ranura pegada al cuerpo, y la imagen de esta ranura movible se magnifica por el microscopio y se enfoca en papel fotográfico en movimiento. Cuando una fuerza estática se aplica al cuerpo, la línea básica del trazado se desplaza permanentemente y de esta manera la amplitud del balistocardiograma se puede calibrar. Sobreponiendo el balistocardiograma obtenido por medio del electrocardiograma en la misma película, comparaciones exactas de los dos trazados y la calibración del instrumento eléctrico se pueden obtener.

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Torsion Ballistocardiography: With Special Reference to Patterns in Surgically Amenable Cardiovascular Diseases

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The recoil forces generated in the circulatory system were converted into a momentum (torque) by using a table supported by a single steel bar in its center. With such a torsion ballistocardiograph, information can be obtained on the site of origin of the forces and on their direction, because the amplitude of the table is proportional to the product force times lever arm (distance from the center of rotation), and the latter can be varied by placing the subject in various positions relative to the center of rotation. The limitations of ballistocardiography in general arise mainly from the complexity of the system of three oscillators (heart, body, table) in which the elastic and damping properties of the body are presently unknown. These limitations are discussed.

I. The Mechanics of the Reaction Forces Producing the Ballistocardiogram

THE pulsatile flow of blood and the periodic movement of the heart muscle impart reaction forces upon the body which are measurable either in the resulting movement of the body resting upon a stationary support (Dock's shin type of ballistocardiograph) or as the displacement of a table which is freely moveable in one or more degrees of freedom and upon which the subject has been placed. A discussion of the forces involved will reveal a number of limitations inherent in the ballistocardiographic method:

1. According to Newton's laws, any accelerated mass within the body has its counterpart in a reaction force acting upon the body and consequently will contribute to the ballistocardiogram. There can be no doubt, therefore, that the ballistocardiogram reflects not only the acceleration of the blood during ventricular systole, but likewise movements of the heart muscle itself. A constant force, that is, a force of constant magnitude acting throughout the cardiac cycle, cannot be detected ballistocardiographically because it would merely affect the baseline of the system and the latter cannot be ascertained when the subject lies on the table. In cases, therefore, where a pulsatile increase in flow is superimposed upon a constant flow, the alternant component only will be reflected in the ballistocardiogram.

2. The body represents a closed system and no accelerated mass particle can escape to the outside. The law of the conservation of momentum, therefore, requires that the net sum of the reaction forces during one cardiac cycle must be zero; in other words, the sum of each mass acceleration during one cycle must be followed by a mass deceleration of equal magnitude. From Starr's classic analogy of the suspended room and the man with a waterhose[1] it is obvious that changes in the displacement of the room depend on (a) changes in the reaction force produced by changes in the ejection of water from the nozzle, and (b) on the pattern of deceleration and on the time at which the deceleration of the water particles at the opposite wall of the room occurs. As the deceleration drives the room into the opposite direction, the time relationship between acceleration and deceleration will to a large extent determine the amplitude and pattern of the displacement of the room.

In the case of the heart the pattern of acceleration is a function of the cardiac ejection. The pattern of deceleration and the time lag or phase shift between acceleration and deceleration, however, depend on a variety of factors

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such as dimensions of aorta, flow velocity, site of deceleration, filling and elasticity of the aorta and drainage through the arterioles. The ballistocardiogram resulting from the ejection of the stroke volume has, therefore, at least two components, one produced by the acceleration of the blood and, therefore, a function of the volume-velocity curve of ejection, and the other produced by the deceleration of the blood and no simple or predictable function of the ejection curve at all. The ballistocardiogram is caused by the sum of these two forces and is, therefore, neither the second or third derivative nor any other direct function of the velocity curve of cardiac ejection, and consequently the cardiac ejection curve (or the stroke volume) cannot be derived from the ballistocardiogram.

3. All forces involved are vectors; that means they are characterized by an amplitude and a direction, and at any instant of the cardiac cycle the reaction force F is the vectorial sum of the forces produced by the acceleration or deceleration a of the various masses m. In special cases there might be no resulting force F at all, for example, if two masses m_1 and m_2 are accelerated in opposite directions and m_1a_1 equals m_2a_2. In this case the forces of the two masses are cancelling out each other, and the center of gravity remains at rest.

The ballistocardiogram, therefore, does not only depend on the magnitude of the force components but likewise on their direction and on their time relationship. Their spatial direction is determined by the anatomy of the heart and large vessels, and may be markedly different from individual to individual. Of the total reaction force, the head–foot ballistocardiogram picks up only an unknown fraction, namely, the force components acting in head–foot direction, and this fraction of the total force may vary individually simply due to individual variations in the anatomy of the heart and large vessels.

II. Principle of Torsion Ballistocardiography, Methods and Material

In view of the vectorial nature of the reaction forces, a torsion ballistocardiograph (TBCG), as used in this investigation, offers a number of advantages for the study of the pattern of the ballistocardiogram and its correlation with certain abnormal cardiodynamics, because with this type of ballistocardiograph one can obtain information on the direction of the forces as well as on their site of origin. In principle, the torsion ballistocardiograph consists of a table top which is not supported at the four corners but in its center only by an upright steel bar. The torsion elasticity of this steel bar permits circular movements of the table top around this center of motion. The magnitude (arc) of the circular displacement of the table as the result of an impressed force is proportional to the product of force times lever arm where the latter is the distance between the site of action of the force and the center of rotation.

The introduction of the lever arm makes the ballistocardiograph much more versatile, and by taking tracings with the subject placed in various positions relative to the center of motion one can accentuate the reaction force arising in certain parts of the vascular system. Furthermore, this principle can be used to determine grossly the unknown site of origin of a given force by observing the position where a given wave in the torsion ballistocardiograph will disappear and then will be reversed in direction.

Technical details of the torsion ballistocardiograph are presented in figure 1. The torsion bar, a round steel rod of ¾ inch diameter and 5½ inches length, is welded to the base of the instrument constructed of heavy iron girders. At the upper part, the torsion bar is surrounded by a ball bearing in order to prevent possible bending of the bar under load. The very small amount of dry friction introduced by the ball bearing was found to be negligible. An iron plate at the upper end of the torsion bar is bolted to a similar plate on the table top and all movements of the table top are only possible through the torsion elasticity of the rod. A moveable x-ray tube, not shown in the illustration, was mounted at the base of the instrument so that x-ray films could be taken when the subject was lying on the table and the distance of the various parts of the aorta

from the center of rotation could thus be determined.

The movements of the table top are arcs. However, as their amplitude is only in the order of magnitude of $\frac{1}{100}$ of an inch, they can be considered as straight lines. The displacements of the table are converted into proportional voltage by means of a condenser plate of a carrier frequency circuit, one plate of which is stationary and the other plate of which is connected to the table top in such a way that only movements of the table in the horizontal plane are recorded. The rectified output of this carrier circuit is amplified and recorded by means of the direct current amplifier of a Sanborn Polyviso recorder.

a greater displacement of the table at low frequencies than at higher. Such a falling frequency response, however, should not be confused with a distorted frequency response, because it is quite acceptable as long as the frequency response curve follows a defined mathematic function. The damping and the restoring force of the table used in this study were arranged in such a manner that a $1/2\pi f$ frequency response was achieved. From the equations describing vibrations it can easily be seen that such a response represents nothing else but a mechanical integration.[2]

The $1/2\pi f$ frequency response was realized in the torsion ballistocardiograph used in these investigations by using a table with a natural

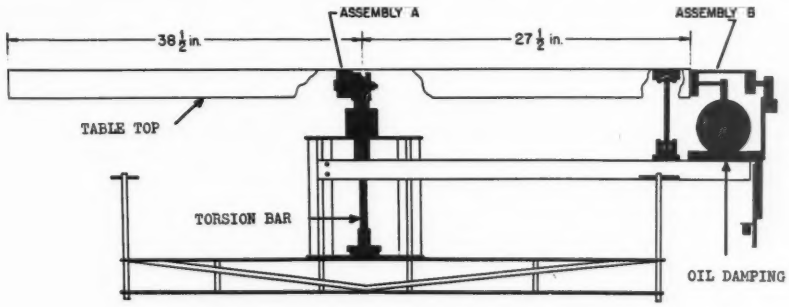

FIG. 1. Schematic side view of the torsion ballistocardiograph.

Human body and ballistocardiograph table represent an intricate system of coupled oscillators, and the mechanical characteristics of both these oscillators must be taken in account when one attempts to decide on the desirable frequency response of the ballistocardiograph table. All present day ballistocardiographs are based upon the assumption that the damping resistance of the human body exceeds the elastic and mass components of its impedance throughout the frequency range under consideration (0 to 20 cycles per second). Under this assumption the possible distorting influence of the coupling between the two oscillators, body and table, can be minimized by selecting an oscillating table which offers a great damping but a small elastic and mass resistance. Owing to the small restoring force, the amplitude frequency response of such a table will not be flat, which means that a given force will produce

undampened frequency of 4 cycles per second and a supercritical damping. The damping consists of two adjustable oil dampers which are entirely free of dry friction, and in which a piston moves with a clearance of $\frac{1}{10}$ of an inch in an oil filled cylinder. The frequency response curve of the table was determined by recording the movements of the table while a sinusoidal force of uniform magnitude was impressed upon the table at various frequencies. The force was produced by a motor driven excenter which was connected by means of a leaf spring to the table top. Each rotation of the excenter impressed a sinusoidal force of equal magnitude upon the table because the amplitude of the excenter was large in comparison to the amplitude of the table. The damping of the table was adjusted until an exact $1/2\pi f$ response of the system was obtained. Changes in the momentum of inertia of the system as

they occur due to different weight of a subject or due to different positions of the person on the table caused only negligible changes in the frequency response.

While small changes in the momentum of inertia (weight and position of the subject) do not affect the frequency response, they affect, of course, the sensitivity of the instrument. A calibration by applying a known force to the table top while the subject lies in position is, therefore, necessary. To this end a mass of 1500 Gm. was attached by means of a spring to the table top, and after the subject was placed upon the table the pendulum was released electrically. The sinusoidal forces impressed upon the table by the oscillating pendulum provided the calibration of the whole system. No attempts were made to express the amplitudes of the table in absolute terms, but before each torsion ballistocardiogram was taken, the attenuation of the amplifier was adjusted in such a way that the table movements due to the oscillations of the calibration pendulum produced waves of exactly 40 mm. in the tracing. Thus the sensitivity of the ballistocardiograph with the patient lying in position was identical in all tracings.

The different lever arms in various positions of the subject relative to the center of rotation, of course, must be taken in account. In each tracing the position of the subject upon the table is indicated by a schematic drawing of the aorta as seen from above. In repeated ballistocardiograms, for example, before and after surgery, the patient was placed upon the table in identical positions, and these tracings are, therefore, directly comparable.

All records were taken in midrespiration and an upward peak in the tracing represents a clockwise rotation of the table top as seen from above; a downswing represents a counterclockwise rotation. All time relations mentioned use the R wave of the electrocardiogram as the point of reference.

In most of the patients a complete cardiovascular work-up was available. Pressures were obtained from the right heart by catheterization; Sanborn electromanometers were used throughout. The electrocardiogram served as the common time reference. Heart sounds and electrocardiogram were recorded simultaneously with ballistocardiogram by means of a multichannel Polyviso direct writer, and the former were intended only as an approximate reference of the duration of systole. Throughout the records these heart sounds are indicated schematically above the electrocardiogram.

III. The Role of the Mechanical Body Impedance

It was pointed out that the torsion ballistocardiograph table used in this study (as well as all other types of ballistocardiographic instruments presently in use) is based on the assumption that the damping resistance of the human body exceeds the elastic and mass components, and that for the frequency range of interest the body impedance does not vary with the frequency. In the course of this study doubts arose as to the validity of this concept. In some individuals with a fast heart rate the ballistocardiogram was found to consist mainly of distorted sinusoidal waves of a frequency of about 5 cycles per second, and these tracings already grossly conveyed the impression of an oscillator resonating at its natural frequency. Even more suggestive were observations in patients with A-V block (fig. 2) where isolated atrial contractions produced series of waves similar to those produced by ventricular contractions. The large amplitude of these atrial waves (marked A in fig. 2) may be explained by the hypertrophy of the atrium in this patient, but it is unlikely that the reaction force due to atrial contraction is of such a long duration (500 milliseconds) and of such a complicated pattern (three up- and downswings). It was suspected, therefore, that these waves do not represent the true reaction forces of atrial systole but rather the resonating mass of the body which was excited by the atrial systole and which continued to vibrate in its resonating frequency. A Fourier analysis* of the waves supported this interpretation. As shown in table 1, the relative amplitude of the harmonics

* The authors are indebted to Dr. Paul W. Schafer and Mr. Fred Berry who made available their electronic wave analyzer.

was very similar in the waves due to the isolated atrial contractions and in those due to ventricular contractions. In both instances the predominant frequencies were those around 4.3 cycles per second, suggesting that both events excited the same resonator, namely, the body mass.

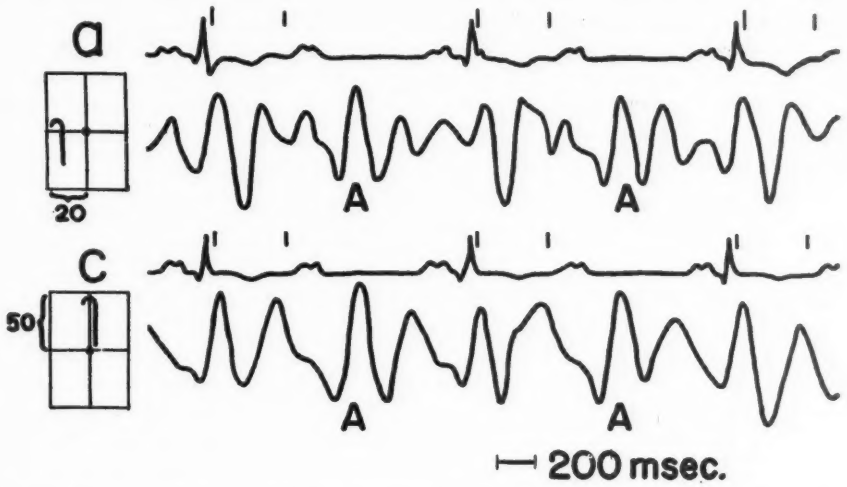

FIG. 2. Electrocardiogram and torsion ballistocardiograph in a patient with AV block and mitral regurgitation. The auricular complexes are marked A.

It seems, therefore, necessary to consider in some detail the factors which may modify the reaction force during its transmission from the site of origin (heart or aorta) to the site of measurement (pick up device of the ballistocardiograph table). For example, the reaction force primarily acting upon the heart is transmitted through the intrathoracic tissues to the bony structure of the thorax and from there through muscles, fat and skin to the table. All these interposed tissues have, from the standpoint of measuring the reaction force, undesirable elastic and damping properties, and it is likely that the original force F will be considerably changed, both in amplitude and phase, during its transmission through these tissues.

A diagram illustrating these factors is given in figure 3. Action and reaction are symbolized by an excenter with one force accelerating the blood and its reaction force acting upon the heart. The intrathoracic tissues are indicated as the "interior coupling" consisting of an elasticity (spring) and a damping. The muscles, fat and skin between the skeleton of the body and the ballistocardiograph table are indicated in the same fashion as "exterior coupling," and finally the table itself has mass, damping, and elastic characteristics which are known while the characteristics of the exterior and interior coupling are unknown. This diagram represents a simplification of the actual conditions, and can be complicated at will by adding, for example, coupled oscillators representing head, arms, and other parts, but this simplification already reveals the very great importance of these factors. Those unfamiliar with such a system may underestimate the influence of the elasticities and dampings, but it must be understood that for any given pattern of force impressed upon

TABLE 1.—*Harmonic Analysis of the Torsion Ballistocardiogram of Figure 2a.*

Harmonic	cps	Relative Amplitude	
		Auric. complex	Ventric. complex
1	1.45	12	29
2	2.9	63	64
3	4.3	100	100
4	5.7	38	24
5	7.1	35	18
6	8.5	25	13
7	10.1	18	2

the system almost any conceivable pattern can be obtained at the writing arm of the table simply by varying the elasticities, dampers and masses of the system. Applied to the ballistocardiographic method this means that even if one knows the characteristics of one's table or measuring device, the recorded ballistocardiogram may have little resemblance to the pattern of the reaction force which one wants to measure.

As long as the damping resistance of the exterior coupling exceeds the elastic and mass resistance, only the amplitude of the ballistocardiograph waves will be altered, but for frequencies where this is not the case, considerable distortions in shape and phase of the waves must be expected. Information on the magnitude of the components of the mechanical body impedance is, therefore, of great importance and represents the most urgent problem in the advancement of ballistocardiography. A true record of the reaction forces can only be obtained after the components of the body impedance have been determined quantitatively. Only then the characteristics of the ballistocardiograph table can be adjusted accordingly, or, if this should prove to be impossible, the ballistocardiogram can be corrected electrically or graphically.

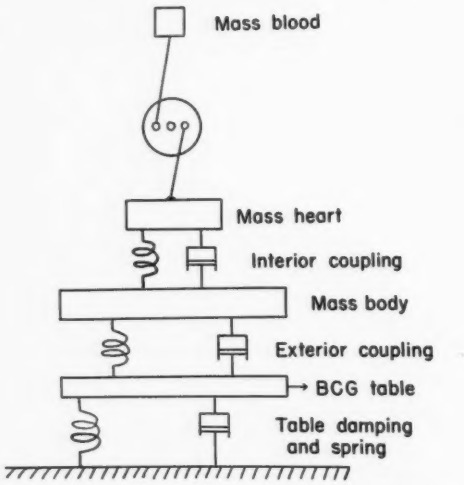

FIG. 3. Diagram of a general mechanical equivalent of the system heart-body-ballistocardiograph table.

For the time being, caution must be exercised in analyzing ballistocardiograms, and it is unwarranted to correlate each spike or deflection of the tracing with a circulatory event. In this study, therefore, more emphasis was placed upon the comparative analysis of the torsion ballistocardiogram in the same individual before and after cardiac surgery, because it is likely that the body impedance in one individual does not change significantly within a few days or weeks.

IV. Clinical Observations

1. The Normal Torsion Ballistocardiogram

A representative example of a normal torsion ballistocardiogram is given in figure 4. The series 4*a–e* shows tracings where the midline of the subject was placed at various points of the *BB′* table axis, and the diagram with each tracing indicates schematically the position of the aorta relative to the axis of the table. The figures in the diagrams represent the distance of the subject's midline from the *AA′* axis in centimeters. In figure 4*a* the longitudinal forces act with a long lever arm and this position is similar to the conventional head–foot ballistocardiogram, that is, a headward force produces an upward deflection of the record.

The transverse forces where studied in the series 4*f–k*, where the longitudinal force was suppressed and the transverse forces were recorded with various lever arms. The position of the aorta relative to the center of rotation is indicated in the schematic diagrams and the figures represent the distance between arch of aorta and center of rotation in centimeters.

The most conspicious wave in the transverse series is the large downswing (fig. 4*f*) which occurs in early diastole and reaches its maximum at 640 milliseconds (after the R wave of the electrocardiogram). The downswing is followed by an upward wave at 840 milliseconds. The waves were present in all normal subjects provided the heart rate was slow enough, otherwise these waves may be fused with and superimposed upon waves related to atrial systole. These waves must originate in or close by the

heart because they disappear when the heart is placed close to the center of rotation, and they are reversed when the subject is shifted farther towards the other end of the table (fig. 4*i–k*). These waves are distinct from the K wave in the longitudinal series, which occurred at 540 milliseconds (fig. 4*a*). Besides this time difference, the K wave is absent in patients with coarctation of the aorta while the transverse waves are present in these patients (fig. 8).

in good agreement with the findings of these authors.

2. Auricular Systole and Isometric Ventricular Contraction

Tracings of patients with A-V block lend themselves to the study of the contribution of atrial systole to the ballistocardiogram. Figure 2 is an example of markedly hypertrophic atrium and has been discussed above. The contraction of a hypertrophic atrium in mitral

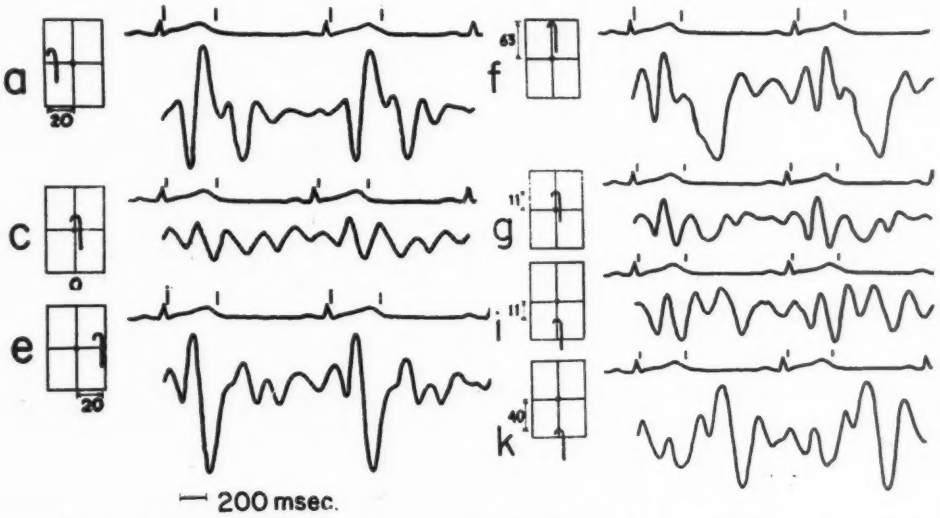

FIG. 4 (*a–k*). Electrocardiogram and torsion ballistocardiogram of a normal subject in various positions relative to the center of rotation as indicated in the diagram at the left of the tracings.

The direction of the forces producing these waves and their site of origin suggest that they are related to the filling of the heart during early diastole, and the downswing (fig. 4*f*) at 640 milliseconds would be produced by the rapid inflow of the blood into the ventricle and the upswing at 840 milliseconds by the deceleration of this blood inside the ventricle. The amplitude of these waves may seem to be too large to be caused by the diastolic filling of the heart, as compared with the acceleration of the blood during cardiac ejection. However, Rushmer and Thal[3] have shown by a cinefluorographic method that the filling of the ventricle during early diastole occurs more rapidly than its emptying during systole and our observations are

stenosis produces marked recoil forces in the transverse direction, as shown in figure 5*b*, and figure 7*b* as a larger upswing almost synchronous with the R wave of the electrocardiogram. This wave must be produced by a force acting from the left to the right at heart level and is definitely related to the atrial contraction because it disappears when such a patient goes into atrial fibrillation as demonstrated in figure 5. The left side tracings represent a patient with severe mitral stenosis in atrial fibrillation and the right side tracing the same patient after conversion to a normal sinus rhythm, and one clearly notes in the left hand tracings the absence of the large wave which is so prominent in the right side tracing. This atrial wave in patients with mitral steno-

sis became smaller and more delayed in some cases following valvulotomy, but remained unchanged in others (fig. 7), and there was no correlation with the success or failure of the operation. It is doubtful whether the acceleration of the blood during atrial systole is responsible for this atrial wave; we are rather inclined to believe that the movement of the heart muscle itself, especially in those cases with hypertrophic atria, and possibly the interruption of the venous inflow, are the main factors in producing the mentioned wave.

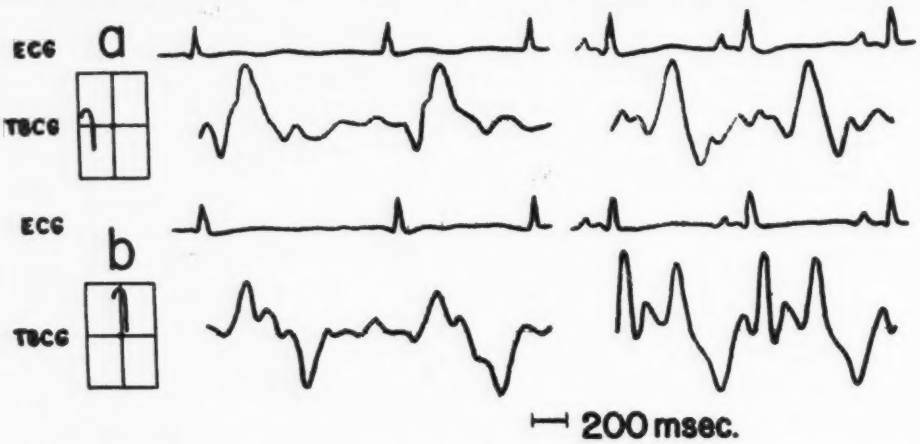

FIG. 5. Effect of atrial contraction on the torsion ballistocardiogram. Electrocardiogram and torsion ballistocardiogram in a patient with mitral stenosis during atrial fibrillation (left tracings) and with normal sinus rhythm (right tracings).

Especially interesting changes were found in four cases of constrictive pericarditis before and after pericardiolysis and they demonstrate an entirely different wave occurring during atrial systole.

Figure 6 shows the torsion ballistocardiogram and right heart pressures of a 14 year old boy with constrictive pericarditis before and after pericardiolysis. The marked increase in the amplitude of the ventricular complex in figure 6*a* after pericardiolysis is very obvious. The position in figure 6*b* accentuates the transverse forces and the postoperative tracing shows the large downswing at 600 milliseconds and all the other features of a normal tracing. In the preoperative tracing this downswing is much smaller, of shorter duration and is followed by a large upswing which is the largest wave of the whole tracing, and this wave disappeared after surgery. The start of this remarkable wave coincides with the P wave of the electrocardiogram, but it reaches its peak (at 70 milliseconds before the R wave) earlier than the peak of the right atrial pressure. We do not believe that this wave is related to the acceleration of the blood from the atrium towards the ventricle but rather to the deceleration of the inrushing blood due to the inextensibility of the ventricles.

3. *The Ventricular Systole*

The relationship between the I and J wave of the ballistocardiogram and cardiac ejection is obscured by a number of factors, of which the distortion of the reaction forces during their transmission through the body tissues and the role of the deceleration already have been discussed. The summation or interference of waves produced by the atrial contraction with those of the ventricular systole has been mentioned in connection with figure 2. Among the other factors which must be considered are the reaction forces originating in the pulmonary circulation, the movement of the center of gravity of the heart muscle, and the opposite direction of the blood movement in the ascending and descending aorta.

Little is known of the contribution of the

pulmonary circulation to the ballistocardiogram. Theoretically, one would expect significant longitudinal forces from the ejection of blood from the right ventricle because the accelerated masses are the same in both ventricles. The transverse forces due to a normal pulmonary circulation are probably not reflected in the torsion ballistocardiogram because the left and right pulmonary artery very likely produce similar and opposite reaction forces which cancel each other. In patients with unilateral pneumonectomy, however, the remaining transverse forces of the opposite side should be demonstrable. Considerable abnormalities were found in the torsion ballistocardiogram of three patients following pneumonectomy. However, these abnormalities did not show a general trend and could not be related to the pulmonary circulation only, but it is probable that unilateral pneumoneetomy induces a great variety of changes, especially by positional alterations of the heart and great vessels.

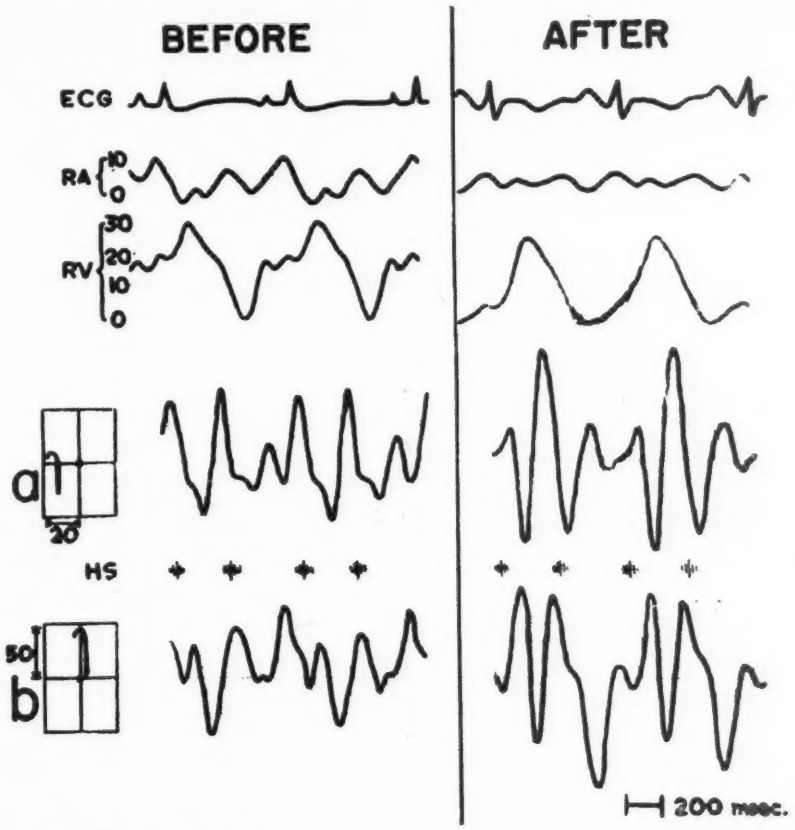

FIG. 6. Torsion ballistocardiogram in constrictive pericarditis (left tracings) and after pericardiolysis. The tracings represent from top to bottom: electrocardiogram, right atrial pressure, right ventricular pressure, torsion ballistocardiogram and heart sounds.

Another important factor affecting the ventricular complex of the ballistocardiogram is the movement of the heart muscle itself. The mass of the heart is considerable compared with the mass of the stroke volume, and, judging from the apex beat, its acceleration and deceleration is likewise significant. We have no way to ascertain the magnitude of these forces because the border movements as measured by

means of electrokymographic or roentgen kymographic methods do not necessarily provide information on the movement of the center of gravity of the heart. Concentric contractions, for example, would not change the center of gravity at all. We tried to obtain information on the reaction forces contributed by the heart movements by comparing torsion ballistocardiograms of patients with advanced mitral stenosis before and after valvulotomy. In these cases the stroke volume was increased significantly after valvulotomy (as measured by the Fick method) and, therefore, an increase in the reaction forces attributable to ejection of the stroke volume could be expected, while the mass of the heart remained unchanged. The reaction forces due to the heart movement should, therefore, remain approximately the same before and after valvulotomy, and any changes in the tracing would rather be due to the increased stroke volume. Figure 7 shows the torsion ballistocardiogram of a patient with rheumatic mitral stenosis (grade III) before and after valvulotomy. In the position in which

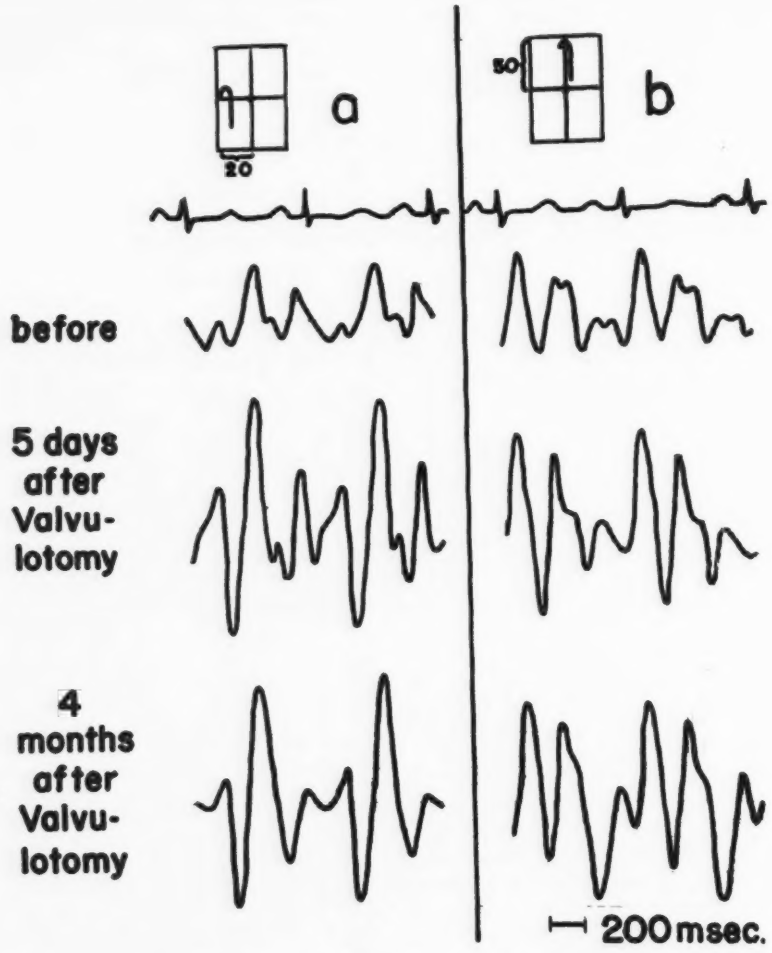

FIG. 7. Electrocardiogram and torsion ballistocardiogram in a patient with pronounced mitral stenosis before and after valvulotomy.

the longitudinal forces are accentuated (fig. 7*a*), the ventricular complex was small and of abnormal pattern, and the change towards normal after surgery is impressive. (Owing to the small complexes before valvulotomy, a greater amplification was used in the tracings demonstrated in figure 7. The sensitivity of the ballistocardiograph was 1.5 times that used in these waves are related to the heart movement itself, both at the beginning of ejection and at the beginning of relaxation. In the same figure 7*b* it will be noted that the deep downswing, normally seen in early diastole and attributed to the diastolic filling of the heart, is almost absent. After valvulotomy this wave appears in normal amplitude and pattern.

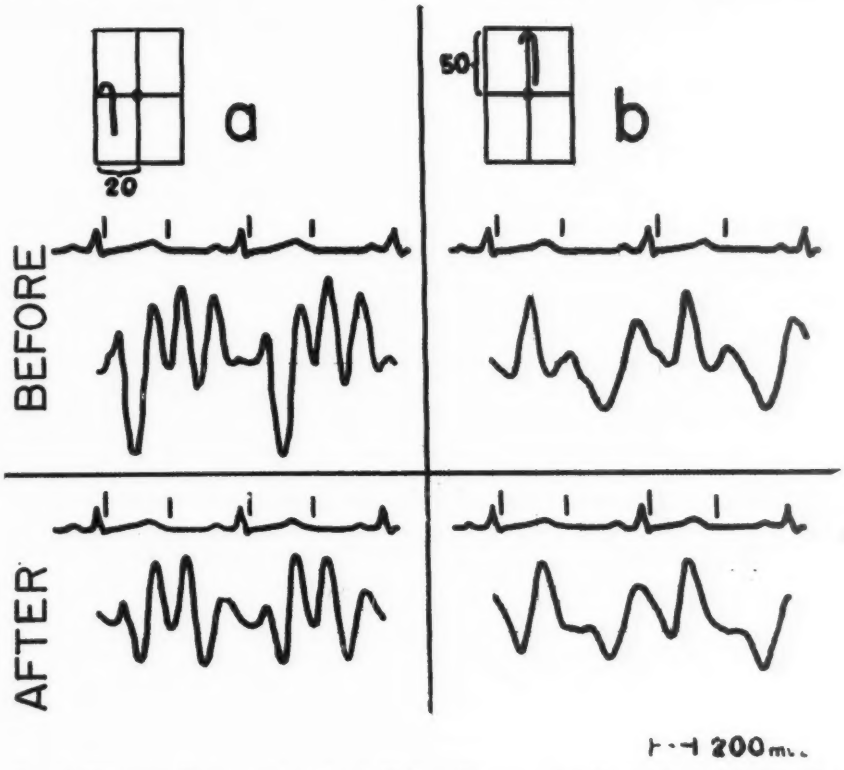

FIG. 8. Electrocardiogram and torsion ballistocardiogram in a patient with aortic coarctation before (upper tracings) and after insertion of a homologous graft.

other tracings.) From these tracings, it appears that the movement of the heart itself does not affect significantly the I and J wave, but is rather noticeable earlier in systole, as demonstrated in figure 7*b*. In these tracings one will notice that the larger upswing occurring 100 milliseconds after the R wave of the electrocardiogram remained unchanged after valvulotomy, and likewise its counterpart, the downswing at the beginning of diastole (460 milliseconds after the R wave). It is likely that

The pre- and postoperative torsion ballistocardiogram in patients with aortic coarctation should provide information on another problematic point of the ballistocardiogram, namely the opposite direction of the flow of blood in the ascending and descending aorta. Instead of explaining the ballistocardiographic waves by analyzing the possible force components in various parts of the heart and vessels, one can more generally consider the ballistocardiographic deflections as caused by shifts of the

center of gravity within the whole body. These shifts of the center of gravity, either in headward or in footward direction, are, of course, mainly produced by shifts in the blood content of the large vessels. From this viewpoint, the I wave must be produced by a shift of the center of gravity into headward direction, and the J wave by one into footward direction. As blood flows at all times in both directions, the shifts of the center of gravity responsible for the I wave must be due to the fact that during the I wave a greater amount of blood is accelerated headwards than toward the feet, and the reverse conditions must prevail during the J wave. The validity of this concept can be examined in patients with aortic coarctation where one would expect the following changes: (a) a greater than normal flow headward during the first half of the systole and consequently a deeper I wave and longer duration of this wave, (b) a delayed and less accelerated (collaterals of smaller caliber) flow footward, and, therefore, a smaller and possibly delayed J wave and the absence of the K wave.

These expected abnormalities were actually observed in all of nine patients with aortic coarctation and were found to be reversible in most of the patients following surgery. Examples are given in figures 8 and 9. Figure 8 represents the torsion ballistocardiogram of a 14 year old girl with a marked coarctation of the aorta, approximately 2 cm. in length. A direct

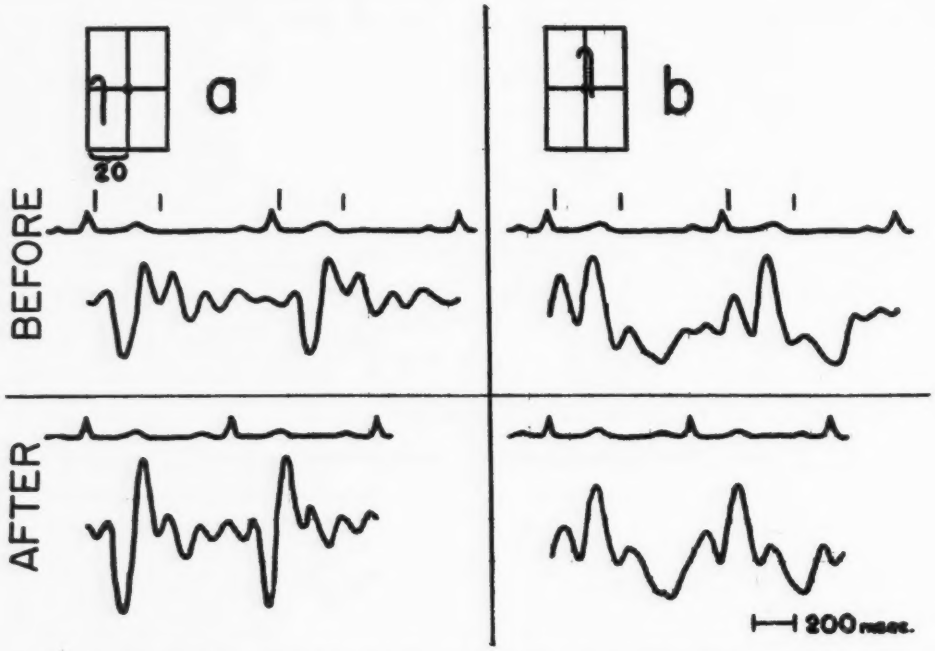

FIG. 9. Electrocardiogram and torsion ballistocardiogram in a patient with aortic coarctation before (upper tracings) and after surgery (end-to-end anastomosis).

end-to-end anastomosis could not be accomplished and a frozen homologous piece of aorta, 5 cm. in length and 15 mm. in diameter, was inserted by end to side anastomosis to the aortic arch. The blood pressure before surgery was 190/120 in the arm and unobtainable in the legs, and after surgery 135/75 in the arm and 110/70 in the leg.

The ratio of the amplitudes I and J which is in normal subjects around 1 to 1.2 was in this case of coarctation 1 to 0.62 before and 1 to 1 after surgery. It will be noted, however, that

the tracing taken three months after surgery is still abnormal, although the blood pressure in the lower extremity was 110/70 mm. Hg.

The persistence of ballistocardiographic abnormalities after surgery in cases of coarctation has been described by Murphy,[4] and we believe that in this case the necessity to insert a graft into the aorta is responsible for the abnormalities in the postoperative tracings.

Figure 9 shows a tracing of a 34 year old man with aortic coarctation and a blood pressure of 160/90 in the upper and 120/90 in the lower extremity before and 130/80 and 125/80 respectively after a complete excision of the coarctation and end-to-end anastomosis was performed. The I to J ratio was 1 to 0.65 before and 1 to 1 after surgery.

4. The Early Diastole

Significant abnormalities of the torsion ballistocardiographic waves in early diastole were observed in patients with patent ductus arteriosus and with aortic insufficiency.

In all of seven patients with patent ductus the changes illustrated in figure 10 were found, namely an upward wave in early diastole. Normally, the upswing of the J wave is terminated at the end of systole and returned to the baseline, but in all cases of patent ductus a strong positive wave was observed at that time. This wave was especially marked in the position demonstrated in figure 10*b*, where it occurred 380 milliseconds after the R wave; that is, it must be caused by a force acting from right to left, but with a headward component as noticed in figure 10*a*. After ligation of the ductus, this wave disappeared in all cases. The vector of this force would agree with the direction of blood flow through the patent ductus; it seems doubtful, however, whether this flow can produce a wave of this magnitude.

Marked abnormalities, especially in the transverse forces, were noticed in patients with aortic regurgitation as shown in figure 11. These tracings are at the same time a good example of the usefulness of recording the torsion ballistocardiogram in various positions, because the tracing in figure 11*a* would pass as normal. This position is similar to the conventional head-foot position, and the ventricular complex

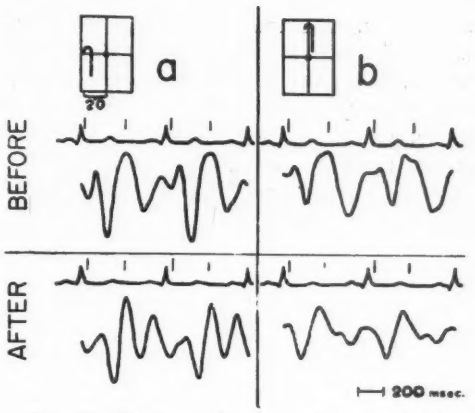

FIG. 10. Electrocardiogram and torsion ballistocardiogram in a patient with patent ductus arteriosus before (upper tracings) and after ligation of the ductus.

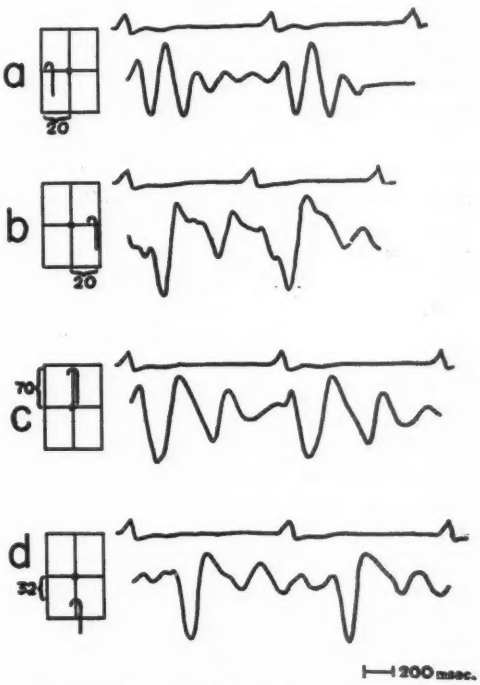

FIG. 11. Electrocardiogram and torsion ballistocardiogram in a patient with advanced aortic regurgitation.

is well developed and of normal amplitude although the patient was suffering from rather advanced aortic insufficiency. In the positions

accentuating the transverse forces, gross abnormalities will be noted, namely, the large negative wave at 400 in figure 11*d* and its positive counterpart in the position demonstrated in figure 11*c*. It is possible that these waves are related to the reversal of flow in the aorta at the closure of the aortic valve and to the regurgitation of the blood.

V. Conclusions

It will be noted that the ballistocardiogram, as a diagnostic aid, is rather superfluous in a number of diseases demonstrated here because they can easily be diagnosed by other means. It was not the aim of this investigation to evaluate the clinical application of the instrument but to investigate more fundamentally how certain defined changes in hemodynamics and especially in the same subject are reflected in the ballistocardiographic tracings. The reproducible and defined response observed in the majority of cases is encouraging in quantitative and qualitative respect. The marked changes in the torsion ballistocardiogram towards normal after valvulotomy in cases of mitral stenosis and the good correlation with other parameters of follow-up studies in these patients seem to justify hopes that the ballistocardiogram eventually may provide semiquantitative information on cardiac function.

It is obvious, from the discussion of the physical principles, that the determination of the stroke volume cannot be achieved under any circumstances by means of the ballistocardiogram, and formulas which use nonmeasurable correction constants are more apt to obscure the results than to elucidate the situation. The amplitude of the I and J wave should, therefore, be expressed in gram-centimeter-seconds^{-2} or as fractions of a known calibration force which had been impressed upon the table while the patient was lying upon the table, and one should have a clear understanding that no wave of the ballistocardiogram represents a single and defined physiologic event, for example, the recoil produced by cardiac ejection.

In view of the vectorial nature of the reaction forces, the recording in at least two directions, that is, the longitudinal and the transverse, seems imperative. The torsional system used in this investigation has the additional advantage that, by means of the effective lever arm, information can be obtained on the site of origin of the forces. With this method more attention can be given to the study of waves other than those of the ventricular complex, and the demonstrated examples of pathologic patterns of these diastolic waves suggest their diagnostic significance.

However, in both approaches, for the quantitative measurement of the cardiac force as well as for the study of the pattern of the ballistocardiogram, it will be necessary to eliminate to a greater extent the influence of the mechanical impedance of the body which has been discussed in detail. Thus, the quantitative determination of the components of the mechanical body impedance for the frequency range of 0 through 20 cycles per second seems to be the most urgent step in advancing the ballistocardiographic method.

Acknowledgments

The authors are indebted to W. W. von Wittern and to Dr. Fritz Haber for advice in the physics involved, and to Dr. Lawrence Lamb for assistance in obtaining the tracings, and to Drs. Paul Schafer and Frederick Kittle who made available a number of their patients and who performed the cardiac surgery.

Sumario Español

Las fuerzas de reculada generadas en el sistema circulatorio fueron convertidas en momento (torque) usando un tablón sostenido en el centro por una sola barra de acero. Con un balistocardiógrafo de torsión de tal descripción, se puede obtener información del sitio de origen de las fuerzas y de su dirección, debido a que la amplitud del tablón es proporcional al producto de la fuerza por el brazo de palanca (i.e., distancia del centro de rotación), y el último puede ser variado moviendo el sujeto en diferentes posiciones relativas al centro de rotación. Las limitaciones de la balistocardiografía en general suscitan de la complexidad de el

sistema de tres osciladores (corazón, cuerpo y tablón) en el cual las propiedades elásticas y apagadoras del cuerpo en el presente son desconocidas. Estas limitaciones se discuten.

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The Significance of the Intermediate Korotkoff Sounds

By SIMON RODBARD, M.D., PH.D.

Except for those sounds that mark the systolic and diastolic blood pressure levels, the murmurs during sphygmomanometry are generally ignored. Our studies suggest that the intensity and duration of these murmurs provide an appraisal of the blood flow into the part beyond the cuff under certain conditions.

THE sounds heard at the brachial artery distal to the point of compression by the sphygmomanometer cuff have been classified into several phases. As the cuff pressure falls from high levels, the onset of a snapping sound characterizes the level of the systolic pressure. With further reduction of the pressure in the cuff the sound changes through an assortment of murmurs and rumbles until finally it becomes muffled and then disappears entirely. The diastolic pressure has been variously designated as related to the sudden marked change in tone as the cuff pressure continues to fall or to the complete disappearance of the brachial sounds.[1] Since the sounds intermediate between the systolic and diastolic levels have not been equated with any specific physiologic event or clinical determinant, they are ordinarily ignored during the blood pressure determination.

Our studies on flow through collapsible vessels[2] suggested that the Korotkoff sounds may depend on the occurrence of flow in the arteries under the cuff, with the production of a fluttering of the vessel walls. If this proved true, attention to the intensity and duration of the intermediate sounds would provide an index of blood flow to the extremity beyond the cuff. To test this hypothesis we undertook studies on patients and on artificial circulation models.

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CLINICAL SURVEY

Preliminary studies were carried out on 75 volunteers and patients on the wards of the Michael Reese Hospital. The essential experiment was carried out as follows: A blood pressure cuff was placed over the upper arm and a stethoscope bell was placed over the brachial artery at the antebrachium. The blood pressure was then taken according to the standard technics and criteria of the American Heart Association.[1] Records were made not only of the systolic and diastolic levels but, when they were clearly heard, of the time of appearance of the intermediate rumble and of the sudden change in tone auguring the diastolic level.

The intermediate rumble usually became audible at a level 5 to 10 mm. Hg below the onset of the snapping systolic sound. It often became intensified as the cuff pressure decreased and occasionally split into a double sound. The rumble then waned and changed suddenly to a soft blowing sound, heralding the diastolic level. At a level only 5 to 15 mm. Hg below this level the sound usually disappeared entirely.

The loudness and intensity of the rumble was notable in all male subjects tested. In some patients the intermediate sounds could be heard only with difficulty. They were often absent or barely discernible especially in nongravid women. They were easily heard in women in the last trimester of pregnancy.

These data lend themselves to the interpretation that the intensity of the intermediate Korotkoff sounds was related in some way to the volume of blood flow to the distal portion of the extremity. In men with good muscular

development of the forearm, the blood flow supplied to this part is greater than in women with lesser muscular development. In pregnant women, generalized vasodilatation is the rule, the extremities apparently sharing in the increased cardiac output.[3] To test this interpretation, experiments were designed to induce an increased or decreased flow through the arm distal to the cuff.

Effect of Reactive Hyperemia and Tourniquet upon Arteriophonograms

In 15 subjects the Korotkoff sounds were recorded by means of a Cambridge phonocardiographic apparatus. The intensity and duration of the sounds were recorded as the cuff pressure fell from above systolic to less than diastolic (fig. 1, *C*). These records made it possible to analyze the sounds objectively after maneuvers affecting blood flow to extremities.*

A simple procedure was used to induce *reactive hyperemia*. The pressure in the sphygmomanometer cuff was raised above the systolic pressure (250 mm. Hg) in order to obstruct the blood flow beyond the cuff. The patient was then directed to open and close the fist of the affected arm 50 times in about 35 seconds. The cuff pressure was then allowed to fall as in the usual blood pressure determination. This procedure had no effect on the systolic and diastolic pressures, but the intermediate rumble was markedly intensified and prolonged in all instances (fig. 1, *E*).

Observations were also made on the Korotkoff sounds during obstruction to flow through the arm. For this purpose, a *tourniquet* cuff was placed immediately distal to the stethoscope bell. This tourniquet cuff was then inflated to 250 mm. Hg. Blood pressure determinations were then made as usual. The tourniquet procedure had no effect on the systolic and diastolic pressures, but in all instances the intensity and duration of the Korotkoff sounds were markedly diminished (fig. 1, *T*).

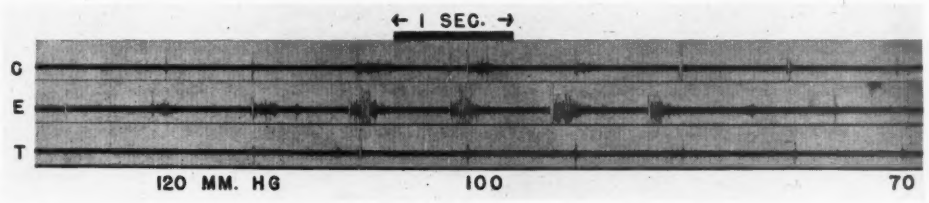

FIG. 1. Phonoarteriograms obtained on a normal subject. Record *C* (control) shows the sounds recorded in a resting subject while the cuff pressure was permitted to fall rapidly as noted in the calibrations given in millimeters of mercury at the bottom of the figure. Time is in 0.04 second.

Record *E* (exercise) was obtained after the sphygmomanometer cuff pressure had been raised and kept at 250 mm. Hg for 35 seconds, with the fist being opened and closed 50 times in this time period. Note the increased intensity and duration of the Korotkoff sounds in this reactive hyperemic period, compared with the control.

Record *T* (tourniquet) was obtained when a tourniquet was in place immediately distal to the microphonic pickup. Note the marked diminution in intensity and duration of the Korotkoff sounds in this period of reduced flow, compared with the control. (Discussed in text.)

MODEL EXPERIMENTS

Further studies were undertaken on a model utilizing a segment of soft-walled Penrose tubing as an "artery" (fig. 2). The "artery"

* The aural interpretation of intensity of a sound is due to a combination of amplitude of vibration, duration and frequency spectrum. This is particularly true in sounds of short duration as may occur in the Korotkoff or heart sounds. Graphic recording with standard phonocardiographic equipment provides a measure of the duration of the sound but does not always give an entirely adequate representation of the frequency-time spectrum or of the subjective interpretation of "intensity."

was enclosed in a glass chamber so that it could be partially compressed by applying air pressure by means of a sphygmomanometer bulb. The cuff pressure was measured with a manometer attached to a side arm of the glass chamber. The arterial pressure was provided by maintaining a column of water at a fixed level above the artery.

The pressure in the cuff was then raised above the level of the supply reservoir. A small but definite volume of water flowed through

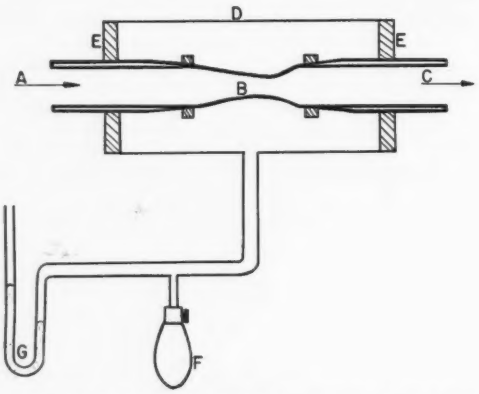

FIG. 2. Diagram of model employed. Flow takes place under a driving head, A, through a rigid tube to the "arterial" segment, B, and then out through the rigid portion, C. Cylinder D encloses the segment ABC. E are rubber stoppers inserted into each end of cylinder, D, with holes permitting tubes A and C to pass through. F is a syringe bulb used to increase pressure in the glass cylinder chamber, the pressure being indicated in manometer G. (Discussed in text.)

the "artery," the amount depending on the level of the cuff pressure (fig. 3).

The cuff pressure was then permitted to fall steadily. When the cuff pressure was exactly equal to the lateral pressure at the inlet tube to the elastic segment, the walls of the "artery" began to vibrate, producing an audible murmur and a palpable thrill. Observation of the segment by stroboscope or high speed cinematography revealed a regular fluttering of the wall at rates varying from 20 to 100 per second.

The production of sound was absolutely dependent on the occurrence of flow through the artery (fig. 4). The intensity of the sound was associated with the height of the supply reservoir. When the flow was increased, as could be done by providing a higher "arterial" pressure, the intensity of the sound was also increased. When flow was stopped the sound

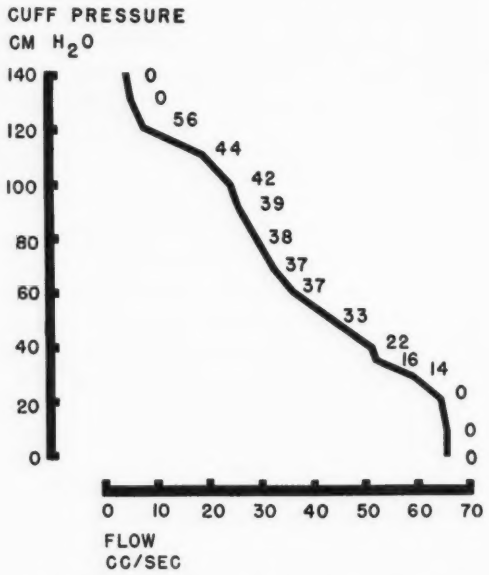

FIG. 3. Flow through the elastic segment illustrated in figure 2. Flow is maintained by a driving head arranged to provide a lateral pressure of 120 cm. H_2O at the inflow to the "artery." Vertical axis represents cuff pressure (sphygmomanometer) in centimeters of water. Horizontal axis gives flow in milliliters per second. The numbers on the curve represent the fundamental frequency of flutter of the "artery" at different degrees of compression indicated by the vertical axis. This value was obtained with the use of the stroboscope. When cuff pressure is higher than driving (arterial) pressure, a small flow occurs, but no murmur is produced (flutter frequency equals zero). When cuff pressure falls below lateral pressure, flow continues to increase, but at a different slope, and the murmur is heard with fundamental frequencies indicated by the numbers alongside the curve. At a critical lower cuff pressure the murmur suddenly ceases. Below the critical value, cuff pressure has little effect on flow. (Discussed in text.)

also stopped. The frequency of flutter, and the fundamental pitch of the sound, were dependent on the cuff pressure, that is, upon the degree of compression of the elastic segment. As the cuff pressure was permitted to

fall, a critical level was reached, usually about 20 cm. H_2O, below which the murmur and thrill ceased abruptly.

Discussion

When the auscultatory method of blood pressure determination was first described by Korotkoff,[4] many attempts were made to explain the mechanism of the sounds. These explanations have included attributing the sounds to the passage of the blood pressure wave, causing the opening of the compressed artery and producing a slapping tone,[4] to water-hammer pulses,[5] to vibrations produced by a change in the form of the compressed vessels,[6] to conversion of the compressed area of the arm into a resonating mass,[7] and to waves reflected from the point of occlusion.[8] Other factors have been implicated in the production of the sounds heard in sphygmomanometry, including turbulence, impact and recoil.[9]

Our present results suggest that the flutter mechanism with the production of murmurs and thrills is derived from the operation of the law of conservation of energy. In brief, this law states that the energy of a volume of fluid may be considered to be the sum of the energy expressed as lateral pressure, plus the kinetic energy of movement. As applied to the artery under the cuff, the following events take place: The artery is partially constricted by the pressure in the cuff. As blood flows through the stenotic portion, its velocity must increase. The increase in velocity results in a reduction in lateral pressure energy at the constricted site. In consequence, the lateral pressure at this point falls, the walls tend to move closer together, and the degree of constriction increases. The velocity of the stream through the constricted area increases further, the lateral pressure is reduced still more and the process of constriction becomes more marked. This continues until the vessel is almost entirely closed. At this point, velocity drops toward zero and all the energy of the column becomes available as lateral pressure. The walls of the constricted portion are then momentarily blown apart. Then the process of increased velocity with its progressive constriction begins again and the cycle is repeated. These flutterings of the walls are suggested as the mechanism of production of murmurs and palpable thrill. When the cuff pressure is above arterial pressure, a slight flow takes place but no flutter is produced.

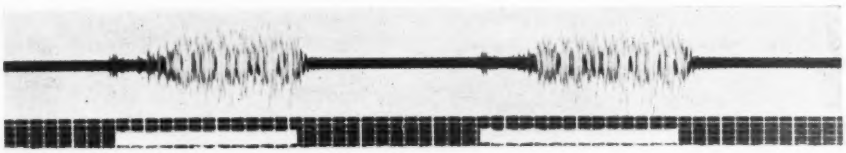

Fig. 4. Phonogram obtained in model experiment. The horizontal white bars show two periods during which water was permitted to flow through the elastic segment of the apparatus described in figure 2. Flow was obstructed in the intermittent periods. Time is in 0.04 second. Sound is noted in the upper tracing shortly after flow begins and disappears shortly after flow ceases. (Discussed in text.)

When cuff pressure has fallen to levels at which no stenosis is produced, flutter is again absent since there is no site of high velocity flow.

In the case of sphygmomanometry the fluttering is probably produced at the site of partial constriction of the artery underneath the cuff. The flow through the arterial segment under the cuff, when arterial pressure is greater than cuff pressure, is presumed to throw the walls into flutter producing the Korotkoff sounds. The experiments with the model suggest that the greatest flutter activity occurs at the distal end of the artery under the cuff. This may account for the fact that the sounds are loudest at this point.

The present study suggests that the duration and intensity of the Korotkoff sounds are related to *flow* through a segment of collapsible vessel. Reduction of flow produced by placement of a tourniquet beyond the point of auscultation results in a diminution or even

elimination of the sounds. An increase in the volume of flow brought about by the production of a reactive hyperemia causes an intensification and prolongation of the murmurs. Similar effects can be illustrated repeatedly in the model. The intensity and duration of the Korotkoff sounds, therefore, may be considered to provide a rough, but perhaps useful, appreciation of the volume flow through the arteries under the cuff. This volume blood flow depends, of course, on the resistance to flow through the vascular bed of the extremity, provided arterial pressure is constant.

In other studies[10] we have demonstrated that a rough index of flow through peripheral arteries can be obtained by appropriate analyses of oscillometric pulsations. A combination of the technic described in the present communication and that utilizing oscillometric pulsations may provide a simple clinical appraisal of flow through the vessels of the extremities, or, conversely, of the peripheral resistance provided by the vascular bed of the extremity. This may perhaps be achieved by noting simultaneously the intensity of the murmurs and the oscillations of the sphygmomanometer mercury column or aneroid indicator.

Summary

Conditions favoring blood flow (reactive hyperemia) through the arteries under the sphygmomanometer cuff increased the intensity and duration of the sounds heard during auscultatory measurement of the blood pressure. Conditions reducing flow through the arteries under the cuff, as by the application of a tourniquet distal to the stethoscope pickup, decreased the intensity and duration of these sounds. The murmurs heard over the artery are shown to be produced as a result of the dynamic pressure-velocity relationships resulting from partial constriction of the vessels by the cuff pressure. The intensity and duration of the Korotkoff sounds, therefore, can be used to appraise the blood flow into an extremity.

Sumario Español

Excepto por los sonidos que indican los niveles de presión sistólica y diastólica, los ruidos presentes durante la esfigmomanometría son generalmente ignorados. Nuestros estudios sugieren que la intensidad y duración de estos ruidos proveen un estimado de la circulación de sangre a la parte distal de la banda pneumática bajo ciertas condiciones.

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CLINICAL PROGRESS

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Vectorcardiography

By G. E. BURCH, M.D., J. A. ABILDSKOV, M.D., AND J. A. CRONVICH, M.S.

THE CONCEPT of the vectorcardiogram was first stated by Mann[1] in 1920. He obtained the trace by manually plotting several successive instantaneous vectors from the standard leads of the electrocardiogram by the method described by Einthoven, Fahr and de Waart[2] in 1913 for determination of the mean manifest potential. This was accomplished by plotting vectors determined from points considered to be simultaneous on the QRS complexes of two of the standard leads of the conventionally recorded electrocardiogram. A trace was then made which began at the origin of the plot and coursed through the termini of the successive instantaneous vectors and ended at the origin of the plot after passing through the terminus of the vector which appeared last in time in the series. Because this trace incorporated data from several leads of the electrocardiogram into a single "loop," Mann called it the "Monocardiogram."

This method of manual construction of the monocardiogram was applied to the waves of auricular depolarization (P waves), waves of ventricular depolarization (QRS complexes) and waves of ventricular repolarization (T waves). Because the resultant traces were all loops of variable shapes, the traces were referred to as P loops, QRS loops and T loops. As is known from the concepts of spatial orientations of the vector quantities, these were projections of spatial loops upon the frontal plane. In fact, Bayley[3] attempted to standardize nomenclature and symbolic representation of the spatially oriented loops by introducing sÊ into the symbols for the loops, the Ê to indicate electric quantities of vectorial (^) nature and the "s" to indicate that these are spatial in orientation. Therefore, today, P sÊ-loop, QRS sÊ-loop and T sÊ-loop indicate the loops as they appear oriented in space, and P Ê-loop, QRS Ê-loop and T Ê-loop indicate the frontal plane projections of the respective spatial loops, unless otherwise stated.

It is of interest to mention that Fahr,[4] using a method of vector analysis, recognized the error in identification of right and left bundle branch currents at that time. These observations, which were later confirmed by Barker, Macleod, and Alexander,[5] provide an early example of the usefulness of vector methods applied to the electrocardiogram.

The manual method of obtaining the monocardiograms graphically was tedious and inaccurate. Mann, therefore, attempted to employ the cathode ray oscilloscope to obtain "monocardiograms" directly but found the cathode ray tubes of that time unsatisfactory for the purpose. He then constructed an ingenious three-coil galvanometer capable of responding to the potential differences of the three standard leads simultaneously.[6] Despite the inevitable mechanical limitations of such an instrument, it was successfully employed to obtain direct recordings. Probably because of the difficulties of manual graphing and the difficulties of mechanical or automatic recording, the monocardiogram was ignored by most observers for many years. Then successful use of the cathode ray oscilloscope for automatic recording was reported by Schellong[7] in 1936

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From the Department of Medicine, Tulane University School of Medicine, the Department of Electrical Engineering, Tulane University of Louisiana, and Charity Hospital of Louisiana at New Orleans.

and by Hollmann and Hollmann in 1937[8] and Wilson and Johnston[9] in 1938. Wilson and Johnston suggested the name *vectorcardiogram* as more descriptive than "monocardiogram."

Following introduction of the use of the cathode ray oscilloscope to record the vectorcardiogram, there was little study of such records for several years. Interest has revived during the past few years as an inevitable result of the trends in electrocradiographic research and because of greater availability of suitable apparatus. Notable improvement in the design and construction of both cathode ray tubes and the necessary vacuum tube amplifiers has been made since 1937. Study of the vectorcardiogram has developed with vigor recently because of growing recognition that spatial analysis of the electric phenomena associated with the heartbeat is likely to yield information not furnished by the conventionally recorded electrocardiogram.

As indicated previously, Mann employed the method of vector plotting introduced by Einthoven, Fahr and de Waart[2] and later used by Williams [10] for obtaining the "vector diagram." This method employs the equilateral triangle of Einthoven as the reference system and results in a trace of the projection of the spatial vectorcardiogram upon the frontal plane. Mann later suggested that electrocardiographic leads be taken from appropriate electrode sites to allow plotting a "transverse monocardiogram," in effect a projection of the spatial vectorcardiogram upon a transverse plane. Arrighi[11] made observations with leads from electrode sites defining a three-dimensional reference frame, and Wilson, Johnston and Kossman[12] introduced the equilateral tetrahedron as a spatial reference frame.

During the past five years the number of reports of both basic and clinical studies relating to the vectorcardiogram has increased. The studies are too extensive to permit a complete review in this presentation. Among the many observations are those by Duchosal and Sulzer,[13] Schellong,[14] Vastesaeger and Rochet,[15-17] Burch and collaborators,[18-24] Burger and van Milaan,[25-27] Donzelot and Milovanovich,[28] Den Boer,[29] Jouve and co-workers,[30] Milnor and co-workers,[31] and Grishman and Scherlis.[32] Selected references to the observations made by these workers and others will be cited in the remainder of this text.

Methods in Vectorcardiography

Graphic construction from electrocardiographic leads and use of the cathode ray oscilloscope constitute the two main methods in use today to obtain the vectorcardiogram. There is no doubt that the latter is the method of choice. Construction of vectors from leads of the electrocardiogram, even when they are recorded simultaneously, is subject to considerable error. It has been shown by oscilloscopic recordings that shifting the time phase of two electrocardiographic leads by as little as 1 millisecond may appreciably alter the contour of a normal vectorcardiogram resulting from the same set of potential differences and may actually change the direction of inscription of a plane projection of a QRS sÊ-loop of normal duration.[33] Since the temporal scale conventionally employed in electrocardiography does not permit distinction of such small intervals, vectorcardiograms derived by manual graphing from electrocardiograms are likely to be erroneous. Vectorcardiograms derived from electrocardiographic leads which are not simultaneously recorded are obviously subject to even greater error.

The use of precordial leads of the electrocardiogram to indicate the direction of spatial vectors, whether they be successively obtained from a single complex to record a spatial vectorcardiogram or from average values of complexes to obtain a spatial mean electric potential, introduces possible errors related to the proximity of the exploring electrode in addition to errors in construction described in the preceding paragraph. This is considered in greater detail under the discussion of the relation of the electrocardiogram to the spatial vectorcardiogram.

Methods of Recording. Details of the methods for recording the vectorcardiogram will not be presented here. The preferred methods involve the use of the cathode ray oscilloscope as the recording "galvanometer." Technics differ, depending on the amplifier circuits, photographic equipment, reference frame, and special

switching devices for automatic recording of elected aspects of the trace which are employed. Although suitable cathode ray oscilloscopes exist, there is room for considerable improvement in electric circuits, in simplification of procedures of photography, and in interpretation of recordings. Detailed information of accomplishments existing today may be obtained by consulting the original publications.

Permanent recordings of the trace impressed upon the screen of the cathode ray oscilloscope may be obtained by photographic technics. The usual practice involves photographing plane projections of the vectorcardiogram of a single cardiac cycle. A 35 mm. camera and film are satisfactory. Although larger film has many advantages, its cost is proportionately greater. By means of suitable switches and other devices it is possible to record automatically any selected portion of the vectorcardiogram or successive complexes with automatic advancement of the film in the camera, to make a continuous recording on moving film or to make cinegraphic recordings. The advantages of these and other special photographic procedures are obvious.

Unfortunately, temporal characteristics of vectorcardiographic phenomena are inadequately recorded by the methods commonly employed in this country. Continuously moving photographic film or paper as reported by Donzelot and Milovanovich[28] may permit adequate recording of temporal data. At present it seems that if vectorcardiography is ever to attain as extensive application in clinical cardiology as electrocardiography, the registration of time in the records must be greatly improved.

The cathode ray beam may be interrupted by means of an oscillator circuit, which results in a trace consisting of a broken line. Each segment of the trace represents a given time interval, such as 1/600 second. The interruption may be of such nature that the segments of the trace are comet-shaped, with the blunt end in the direction of rotation. This permits easy identification of the direction of rotation. Because the trace may move slowly during parts of the cardiac cycle, especially during inscription of the P and T loops and those portions of the QRS loop near the isoelectric point, timing by means of an interrupted beam without use of continuously moving photographic film or paper is difficult and usually imperfect by this technic.

The vectorcardiogram obtained by methods generally employed today not only fails to record intervals between the various loops of the vectorcardiograms but also fails to indicate those cardiac mechanisms whose recognition requires recording of the electric events of many consecutive cardiac cycles. The use of continuously moving photographic film or paper results in a series of connected scrolls which indicate in a complex fashion voltage variations with time. This method has the additional advantage of clearly indicating the direction of inscription of the component loops. Visualization of the data in space presents special problems, however. Despite this limitation, the method deserves further study.

Stereoscopic recording directly from cathode ray tubes by photographic methods is a promising method of approaching the study of spatial vectorcardiograms. Direct visualization of three-dimensional relationships has obvious advantages over study of plane projections alone. To date three schemes have been utilized to obtain such records. Vastesaeger and Rochet[15] placed electrodes on the shoulders in such a manner as to define two plane projections tilted out of the frontal plane, each recorded on separate oscilloscopic screens. When these were viewed through a stereopticon, a single stereoscopic image was seen. A somewhat similar method was reported by Cronvich and associates,[22] but the rotation out of the frontal plane was accomplished by a simple electric network, thus eliminating the need for placement of additional electrodes and its possible attendant errors. Schmitt[34] has also employed electric circuits to achieve stereoscopic recordings of the spatial vectorcardiogram. By means of special circuits, he was able to view the spatial vectorcardiogram stereoscopically from many selected vantage points. Because of the relatively complex electric circuits, Schmitt's method is unlikely to receive general application at present,

especially since the same information may be obtained with less complex apparatus and circuit arrangements.

Reference Frames

Although there is general accord that study of the electric events associated with the heartbeat in planes other than the frontal is likely to be profitable, there is little agreement concerning the placement of electrodes to define such planes. In one of the earliest studies of "spatial vectorcardiography" Savyaloff[35] placed electrodes at selected points on the body to obtain the projections of the spatial vectors on a transverse plane. Arrighi[11] used electrodes at still different sites to define a three-dimensional reference frame. The equilateral tetrahedron is employed as a spatial reference frame by placing electrodes on the forearms, the left leg, and the back. Rectangular or cubic reference frames, employed by some observers, are defined by means of electrodes placed at selected points on the trunk. The original publications[12, 13, 32] should be consulted for details concerning electrode placements and polarity arrangements.

Considerable error is inherent in all reference systems applied to the human body. Their use necessitates several assumptions which are known to be untrue but which apply satisfactorily within clinically and experimentally defined limits. The human body is not a tetrahedron, rectangular parallelepiped or cube, nor is it a homogeneous conductor. The heart is not a point source of potential. Although it is possible in a given subject to make satisfactory corrections or allowances for some of these "deficiencies" of the human body, the existence of these difficulties must always be remembered. Burger and his associates[25-27] and Wilson and co-workers[36] have attempted to correct some of these difficulties by the tedious process of introducing suitable resistances in the leads, but it does not appear that such elaborate methods are practical except for special circumstances. Since no planar or spatial reference system can be applied to the human body without some intrinsic error, the choice among them must be based partially on other considerations. The selection of a spatial reference system must, therefore, be the result of adequate considerations of the advantages and disadvantages of the various possibilities available. Claims of merit of some systems and claims of disadvantages of others have been advanced by various workers. At the present time there are insufficient data to evaluate these claims adequately. Since different groups of investigators employ different reference frames it is difficult to compare results. In some respects this practice may delay progress, but in others it may be of benefit to the fundamental development of vectorcardiography.

It is contended that spatial vectorcardiograms recorded with the rectangular and cubic systems of electrode placement conform more closely to the configurations predicted from the precordial leads than do those recorded with the tetrahedral reference frame. If this is true, it implies that the precordial lead electrode positions are as remote as the electrode positions which comprise the spatial reference frame. This is in disagreement with the concept of Wilson and associates, whose experiments indicated that the electrode positions employed for precordial leads act as "semidirect" rather than remote points with respect to the heart. It is our opinion that available evidence indicates that the detailed form of the precordial leads cannot be derived from vectorcardiograms recorded with any reference system composed of remote electrode positions.

There is no doubt that it is advantageous, at least at present, to be able to compare vectorcardiograms and electrocardiograms, but there is no convincing evidence that this is particularly applicable to vectorcardiograms recorded by rectangularly shaped spatial reference frames. The rectangular parallelepiped and cubic spatial reference systems of lead placement have the disadvantage of requiring several electrodes on the trunk, which is more inconvenient and somewhat less reproducible than the placement of electrodes on the extremities.

The placement of electrodes to define a tetrahedron has the advantage of utilizing the limbs for three of the electrodes. This is advantageous not only because of greater convenience and reproducibility of electrode

positions but also because those electrode sites which define the frontal plane, constituting the well-known and important equilateral triangle of Einthoven, are the same as those from which the standard electrocardiographic leads are recorded. This is of considerable importance, since it means much general information about both normal and abnormal vectorcardiograms can be obtained from the extensive knowledge already existing in electrocardiography. It seems desirable to exploit all available knowledge to orient vectorcardiography in the field of experimental and clinical cardiology.

The equilateral tetrahedron, therefore, has one more electrode position which is different from those already employed routinely for recording the standard limb leads in electrocardiography. This electrode is placed on the back of the thorax, 3 cm. to the left of the spinous process of the seventh dorsal vertebra. The same electrode positions may be considered to define an isosceles tetrahedron. The difference in the two systems lies in the assumption concerning the location of the center of the dipole representing the electric activity of the heart. The four faces of the equilateral tetrahedron are assumed to be equilateral triangles, each side and each plane surface being treated in the same fashion that the frontal plane equilateral triangle of Einthoven is applied in clinical and theoretic electrocardiography today. The advantages of this reference system have been described and discussed in detail elsewhere.[33]

The Relationships of the Electrocardiogram and the Vectorcardiogram

Even though much general information about the form of the vectorcardiograms can be inferred from electrocardiograms and vice versa, there are definite differences in the data each presents directly. The electrocardiogram presents scalar quantities, that is, magnitude and sense are represented. The vectorcardiogram presents vector quantities directly, that is, direction, magnitude and sense are indicated. Vector quantities can, of course, be derived from two or more electrocardiographic leads, but unless a greatly expanded time scale and simultaneous and satisfactory recording of the leads are used, they are only gross approximations of those indicated directly by the cathode ray tube. Therefore, even though the standard electrocardiographic leads and the frontal plane projection of the spatial vectorcardiograms are recorded from the same electrode sites, the form of the spatial vectorcardiogram cannot be accurately derived from the electrocardiogram unless two of the leads are recorded simultaneously and at a much higher film speed than is commonly employed. Thus, even plane projections of the spatial vectorcardiogram contain data which are not available in the electrocardiogram. Whether or not the additional information furnished by the spatial vectorcardiogram will prove to be clinically useful is not yet evident. It does provide information of considerable value for understanding the fundamental principles of the electric events associated with the heartbeat.

Relation of the Spatial Vectorcardiogram to the Precordial Leads

In the past the precordial leads have been utilized to a limited extent in conjunction with the limb leads to indicate the spatial orientation of the mean electric activity associated with the heartbeat. More recently attempts have been made to extend this type of correlation. Data have been reported to indicate that the same information furnished by the precordial leads is evident in the spatial vectorcardiogram. In fact, it has been stated that the information contained in all electrocardiographic leads may be furnished by the spatial vectorcardiogram. This opinion seems at variance with the concept of Wilson[37] that "the potential variations of a precordial electrode are determined to a very large extent by the potential variations of the elements of ventricular surface nearest it." Evidence for the latter statement was furnished by Wilson's experiments, in which direct leads were compared with precordial leads and found to vary in magnitude but to have similar form. Because of this and other observations, he considered precordial leads as "semidirect" leads, dis-

tinguishing them from leads derived from points more distant from the heart. The concept of semidirect leads has been clinically useful in electrocardiography, as evidenced by the identification and localization of anterior myocardial lesions which are not reflected in a recognizable form in leads recorded from electrodes located at more distant points on the body.

It is evident that any contention that electrocardiographic or vectorcardiographic records of the electric events associated with the heartbeat, even though recorded from different electrode positions, are not significantly different from each other must logically indicate that the electrode positions are not significantly different. Furthermore, if the electrode positions are not significantly different, then the potential variations at the respective electrode positions must be correspondingly similar. If all the precordial leads are obtainable from vectorcardiograms obtained with the cubic, rectangular, or tetrahedral reference frames, then the precordial electrode positions for *all* the precordial leads must be equally remote. Experience with the precordial leads in conventional electrocardiography does not bear out such contentions. At present it seems reasonable to state that although it is possible that the spatial vectorcardiogram contains some of the information contained in the precordial leads, differences must exist because of electrode positions.

Limitations of the Vectorcardiogram

Although the range of experimental and clinical usefulness of the vectorcardiogram has not yet been defined, it is apparent that certain limitations exist. For example, temporal characteristics, as previously mentioned, are not adequately recorded. With recording methods commonly employed, the duration of complexes is imperfectly registered, and the intervals between loops or complexes as well as the cardiac mechanism are not shown at all. These deficiencies can be overcome by recording on moving film, but the advantages of a single three-dimensional representation of the electric phenomena of the cardiac cycle are then lost. The probability that semidirect electrocardiographic leads provide information which cannot be obtained from the spatial vectorcardiogram constitutes another limitation of the vectorcardiogram. These considerations indicate that if the spatial vectorcardiogram is to have clinical usefulness in the near future, it will be in the role of a supplement to the conventional electrocardiogram. The original papers may be consulted for further details of the possible applications and limitations of spatial vectorcardiography to experimental and clinical cardiology.

The Spatial Vectorcardiogram and Conventional Electrocardiogram and Clinical States

No good purpose would be served by a description of the spatial vectorcardiographic configurations and orientations for normal and abnormal states, primarily because they would differ for each of the spatial reference frames employed in recording. The reader must, therefore, consult the original papers to obtain such data, remembering always that, although there is some correspondence, the patterns hold only for the reference system employed. Obviously, there must be standardization of electrode positions in vectorcardiography.

We have employed the equilateral tetrahedron as the spatial reference frame for reasons reported in detail elsewhere. Our studies of clinical cardiologic states have indicated that:

(1) The spatial vectorcardiograms of normal young adults were of two main types or patterns. The majority, 88 per cent, of normal QRS sÊ-loops had a smooth elliptoid configuration in which the width was less than one-third the length, and the majority of the area enclosed lay anterior to the iso-electric point. For purposes of description, these loops have been labeled as "type 1." The remaining 12 per cent had a more complex configuration classified as "type 2" and characterized by the enclosure of a wider total area and a larger area behind the isoelectric point than in the "type 1" records. Most normal T sÊ-loops also had an elliptoid form, but in a few instances a roughly circular form was encountered.[38] The wide variations of the various plane projections of the spatial vectorcardiogram were due not

to large differences in the spatial vectorcardiograms among individuals but to differences in spatial orientation of two easily identifiable fundamental patterns. Other rarer patterns may exist, since only several hundred normal subjects of a narrow age group have been studied. Furthermore, the fact that only a small number (only two defined to date) of fundamental spatial vectocardiographic patterns exists suggests that (a) the orders of depolarization and repolarization of the heart of man are similar, or that (b) the extracardiac tissues which influence and determine the electric fields around the heart are fundamentally similar, or that (c) both of these phenomena are true. That these phenomena may be genetically controlled is an important possibility deserving study.

(2) The spatial vectorcardiograms in right and left ventricular hypertrophy were characteristic.[33] The pattern of hypertrophy of the right or left ventricle could be identified even in the presence of complete right or left bundle branch block. Hypertrophy could be recognized with greater certainty from the vectorcardiogram than from the conventional electrocardiogram. Many more recordings with postmortem correlations will be needed before the reliability of spatial vectorcardiography can be fully evaluated in the diagnosis of right or left ventricular hypertrophy, especially when it is slight in amount and not detectable roentgenologically or by other clinical means.

(3) The spatial vectorcardiograms of complete right or left bundle branch block and of myocardial infarction in various areas of the heart were of a sort already predicted from conventional electrocardiographic leads.[33] The initial portion of the QRS sÊ-loop was spatially oriented as already known from electrocardiograms.[39, 40] Much more extensive study of bundle branch block and myocardial infarction is required before the value of spatial vectorcardiography in these states can be determined. Thus far it has not been shown to offer any advantages in these states alone. It appears that the presence of right and left ventricular hypertrophy with these three cardiac states may be detected more readily by vectorcardiography alone than by electrocardiography alone.

(4) Many more studies with adequate postmortem examinations are necessary before vectorcardiography can be considered clinically useful. At present it remains an *experimental* procedure.

Summary

Both theoretic considerations and actual studies suggest that spatial vectorcardiography will eventually have practical applications. It is likely to furnish clinically useful information in addition to that provided by conventional electrocardiography. This is a statement of probability, however, and has not yet been established, nor have the circumstances in which it may apply yet been defined. For this reason the current status of vectorcardiography is properly that of a research method, not yet suitable for general clinical application.

Many technics have been employed to obtain the vectorcardiogram. The graphic derivation of vectorcardiograms from electrocardiographic leads is of historic interest only. The use of the cathode ray oscilloscope with suitable amplifiers is the method of choice. Many modifications of technic, such as recording on moving film, recording of successive complexes, and stereoscopic recording, are possible with the use of the cathode ray oscilloscope. It is not yet apparent which recording technic will prove to be most informative, so that studies with a variety of technics seem advisable.

Several systems of electrode placement have been advocated for obtaining the spatial vectorcardiogram. Since the application of any geometric reference frame to the human body necessitates several assumptions which are not actually true, it appears that the choice among reference frames cannot be made on the basis of their intrinsic validity. We are of the opinion that the equilateral tetrahedron introduced by Wilson and associates[12] offers advantages over other reference frames because:

(1) Only one electrode is necessary in addition to those employed to obtain the standard electrocardiographic leads.

(2) Electrodes are easily applied, and their positions are readily reproducible.

(3) The knowledge already available from experience with the standard leads of the electrocardiogram may be applied to spatial vectorcardiography.

(4) Each of the four surfaces defined by the electrode positions is an equilateral triangle.

(5) The disadvantages of this reference system are common to those of other proposed reference frames.

Variations of the spatial vectorcardiogram in normal man and in man with a variety of disease states have been studied by several groups of investigators with a variety of technics. These studies are of considerable importance, but as yet nearly all lack pathologic confirmation of the presence, site and size of suspected lesions. These data must be obtained and thoroughly correlated with the vectorcardiogram before vectorcardiography can be employed with certainty in general clinical practice.

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ABSTRACTS

BLOOD COAGULATION

Wessler, S.: Studies in Intravascular Coagulation. I. Coagulation Changes in Isolated Venous Segments. J. Clin. Investigation **31**: 1011 (Nov.), 1952.

Using isolated endothelial-lined segments of veins in dogs, the author studied the problem of intravascular coagulation. It was found that clotting occurred much more slowly when the blood was in contact with endothelium than when it was placed in silicone tubes. It was also noted that a fibrin clot developed prior to the disappearance of demonstrable amounts of prothrombin or the elaboration of measurable quantities of clot accelerators. Attention was called to the clinical implications of such findings.

ABRAMSON

Innerfield, I., Schwarz, A., and Angrist, A.: Intravenous Trypsin: Its Anticoagulant, Fibrinolytic and Thrombolytic Effects. J. Clin. Investigation **31**: 1049 (Dec.), 1952.

There is evidence that trypsin produces fibrinolysis in vitro. This study was undertaken to evaluate the effects of intravenous crystalline trypsin on the protein components of the coagulation mechanism and on the fibrin content of artificially induced intravascular thrombi in rabbits and dogs. Experimental thrombi were made by the injection of sodium morrhuate.

Although shock may develop within 15 seconds following a rapid intravenous injection of trypsin in a dose of only 2,000 units per kilogram, in the present investigation administration of six to eight drops of the solution per minute in rabbits and 30 to 40 drops per minute in dogs did not produce shock for several hours during the course of an infusion, despite massive enzyme concentrations and dose (125,000 units per kilogram in rabbits or 100,000 units per kilogram in dogs). Gross changes in the rabbit ear vein thrombi following intravenous trypsin included a diminution and, in several instances, disappearance of the thrombus in situ, restoration of the local circulation and vessel wall compressibility. Microscopically there was a diminution of fibrin and of cellular and platelet masses, and there was no untoward effect on vessel walls. Control animals receiving saline had no change in their clot. In dogs the prothrombin time changed in relation to the dose. A pronounced decrease in fibrinogen levels was related to the total dose; on the other hand, the titer of antithrombin varied inversely with the quantity of injected trypsin. Coagulation time was increased in doses exceeding 500,000 units. A sharp decrease in blood-clotting viscosity occurred after 50,000 units.

WAIFE

Ratnoff, O. D., and Vosburgh, G. J.: Observations on the Clotting Defect in Amniotic-Fluid Embolism. New England J. Med. **247**: 970 (Dec. 18), 1952.

A case is reported of a patient who died approximately 12 hours after delivery as a result of amniotic-fluid embolism. About 30 minutes post partum, the patient went into shock; shortly afterward she began to bleed from the sites of venipunctures. At this time her blood failed to clot in vitro and blood studies revealed the presence of hypofibrinogenemia, an excess of plasma thrombin-inhibitory activity, and a slight decrease in the number of circulating platelets.

It was suggested that the hemorrhagic phenomena in patients with amniotic-fluid embolism were the result of intravascular clotting.

ABRAMSON

Engelberg, H., and Massell, T. B.: Heparin in the Treatment of Advanced Peripheral Atherosclerosis. A Preliminary Report. Am. J. M. Sci. **225:** 14 (Jan.), 1953.

Patients with obliterative atherosclerosis of the legs received intravenous heparin, 100 mg., two or three times weekly over a period of approximately six months. The treatment was evaluated by means of the digital plethysmograph and by a walking tolerance test to evaluate digital and muscle blood flows respectively. Previous therapy with vasodilator drugs and low fat diets in these patients had failed to influence the disease. Following heparin therapy, a significant increase in digital flow was noted in 8 of 14 extremities. In 8 out of 10 cases an improved walking tolerance was observed. Intermittent claudication was improved in 9 of 11 patients with this symptom. Cessation of therapy resulted in a recurrence of symptoms in four to eight weeks. Of the possible mechanisms of action discussed, the authors feel that the reduction of large serum lipoprotein to smaller molecules of lower S_f rates after heparin administration may account in some way for the observed benefits in walking tolerance and digital blood flow. Heparin is suggested as a promising form of therapy for peripheral arteriosclerosis.

SHUMAN

CONGENITAL ANOMALIES

Rogers, H. M., Rudolph, C. C., and Cordes, J. H., Jr.: Coarctation of the Aorta in Infancy. Report of Two Cases with Death from Left Ventricular Failure. Am. J. Med. **13:** 805 (Dec.), 1952.

Left ventricular failure and death occurred in two young infants with coarctation of the aorta. Diagnosis of this anomaly depends upon recognition that it produces heart failure at an early age and that femoral arterial pulsations may be absent. Confusion with congenital intracardiac lesions may result if reliance is placed entirely on electrocardiographic and roentgenographic examinations. Supraventricular tachycardia occurred in one infant. Right ventricular hypertrophy was associated with left ventricular failure in the second infant as a result of the need for the right ventricle to function as a systemic ventricle in the presence of coarctation proximal to the ductus arteriosus. Adequate collateral circulation was absent in both patients.

HARRIS

Joly, F., Folli, G., and Carlotti, J.: Comparative Electrocardiographic Study of Trilogies and Tetralogies of Fallot. Arch. mal. coeur **45:** 1108 (Dec.), 1952.

In 88 cases of various types of congenital pulmonic stenosis the electrocardiographic findings were compared with clinical, hemodynamic and angiocardiographic data. The electrocardiographic changes consisted in variable degrees of right heart strain and alterations of the P wave which could be correlated with pathophysiologic findings.

Maximal right heart strain—inverted T waves in II and III and upright QRS and negative T waves across the precordium—was found in cases in whom a tight pulmonic stenosis was indicated by enlargement of the heart, right ventricular pressures exceeding those in the systemic circulation, and, in the presence of an auricular septal defect, a considerable right-to-left shunt with marked arterial desaturation. In cases of tetralogy, pseudotruncus and in instances of moderate pulmonic stenosis without overriding of the aorta, the pattern of right heart strain was less pronounced, and its evidence was found only in the right sided precordial leads. A characteristic "congenital P wave" was almost constant in severe pulmonary stenosis. It was present in one-fifth of the tetralogies and not encountered in moderate or slight degrees of pulmonary stenosis.

The authors conclude that the electrocardiogram is of value in the differential diagnosis of different malformations associated with pulmonary stenosis especially in the presence of cyanosis. The comparative study of hemodynamics and electrocardiographic findings revealed that mechanical factors are of greater importance in the pathogenesis of right ventricular hypertrophy in pulmonary stenosis than congenital anomalies of the architecture of the right ventricular wall as proposed by others.

PICK

Connolly, D. C., Lev, R., Kirklin, J. W., and Wood, E. H.: The Problem of Isolated Valvular Versus Infundibular Pulmonic Stenosis with Particular Reference to Cardiac Catheterization Data and Records Obtained at the Time of Operation. Proc. Staff. Meet., Mayo Clinic **28:** 65 (Feb.), 1953.

Since the development of pulmonic valvotomy for valvular pulmonic stenosis and the subsequent development of technics for correction of infundibular stenosis, increasing importance has been attached to the preoperative differentiation of these conditions, since the type of operation depends on the type of obstruction found at the pulmonic valve. During routine cardiac catheterization it is usually possible to enter the pulmonary artery even when a severe degree of pulmonic stenosis is present. If this is the case, the diagnosis of pulmonic stenosis can then be made by the demonstration of a high systolic pressure in the right ventricle and a low systolic pressure in the pulmonary artery. Fluoroscopic observation of the tip of the catheter and continuous monitoring of the pressure being transmitted through the catheter allow localization of the region in the cardiac shadow at which the change from the high right ventricular pressure to the low pulmonary arterial pressure occurs. Under ideal circumstances, it can also be determined if

this change occurs abruptly in the region of the pulmonic valve. If the latter can be demonstrated with certainty, it is an indication, but not absolute evidence, that the stenosis is of the valvular type. In infundibular stenosis it is frequently possible, by careful manipulation of the catheter during its withdrawal from the pulmonary artery to the right ventricle, to detect an intermediate zone of pressure in the outflow tract of the right ventricle. This finding is characteristic of infundibular pulmonic stenosis and enables a positive diagnosis to be made. It is possible by studies of pressure during operation to provide material assistance to the surgeon during the actual operation. Continuous recording of pressures throughout the operation provides an objective indication as to when the degree of benefit attained justifies cessation of the surgical attack on the stenosis. It has been demonstrated that several repetitions of the surgical maneuver may be necessary before maximal relief of the stenosis can be achieved. Recordings of the final pressure obtained replace subjective impressions by objective measurements of the actual improvement resulting from the operation. It has been the authors' experience that operations for pulmonic stenosis can be carried out more accurately and completely with the aid of pressure recordings made at the beginning of and during the operation.

SIMON

Odman, Per.: The Appearance of the Internal Mammary Arteries in Coarctation of the Aorta. Acta radiol. **39:** 47 (Jan.), 1953.

It is possible to visualize dilated internal mammary arteries in conventional roentgenograms taken in true lateral projection. These are seen close to the anterior thoracic wall as an entirely or partially continuous soft tissue band of varying width. Occasionally double contours of such densities are noted, due to superimposition of the right and left arteries.

Technically, films taken on deep inspiration with high voltage and a relatively long tube to film distance are considered best. Postoperatively these dilated collaterals have been noted to diminish and disappear within a year, in others it may take several years.

SCHWEDEL

Burke, M., and Northoff, F.: Eye Changes In Congenital Heart Disease. Klin. Monatsbl. Augenh. **120:** 351, 1952.

Ophthalmologic studies were made on 74 patients with congenital cardiac defects, before the precise diagnosis was established. Later it was found that 27 had the tetralogy of Fallot, 15 had Eisenmenger's complex, 11 had patent ductus arteriosus, and 21 had various atypical deformities. The children with patent ductus arteriosus and no cyanosis, had no eyeground changes or polycythemia. However, children with the tetralogy of Fallot or cyanotic congenital heart disease had cyanosis of the conjunctivae and retinae, erythema of the optic papillae, tortuosity, and dilatation and darkening of the retinal vessels, particularly of the veins. The degree of eyeground changes corresponded to the severity of the cyanosis and polycythemia. They are compensatory manifestations.

BERNSTEIN

Broadbent, J. C., Wood, E. H., Burchell, H. B., and Parker, R. L.: Ebstein's Malformation of the Tricuspid Valve. Proc. Staff. Meet., Mayo Clinic **28:** 79 (Feb.), 1953.

The essential feature of this condition is maldevelopment of the right ventricle related to apical displacement and distortion of the tricuspid valve. A patent foramen ovale was present in Ebstein's case and this abnormality, or a gross defect of the atrial septum, has been present in the majority of cases. However, these are not an integral part of the anomaly. Of the three cases which form the basis of this report, the diagnosis has been established by postmortem examination in one but, in the other two, the physical findings and the findings on cardiac catheterization appear sufficiently definite to establish the diagnosis.

One case was a well-developed, moderately obese male with cyanosis (grade II) of acral parts and clubbing of fingers and toes. The blood pressure was 110 mm. Hg systolic and 82 diastolic. A systolic murmur with thrill was present in the fourth intercostal space at the left of the sternum and was widely transmitted. The systolic murmur was followed by a short diastolic murmur, and this in turn by a peculiar third sound which resembled a pericardial rub. In the roentgenogram of the thorax the cardiac silhouette was markedly enlarged and pulmonary vascular markings were normal. Evidence was obtained at catheterization which indicated the presence of an atrial septal defect through which a small left-to-right shunt and a larger right-to-left shunt were taking place. There also were two zones of pressure within the "right ventricle," separated by a competent valve mechanism. These findings are best explained by Ebstein's malformation of the tricuspid valve.

SIMON

CONGESTIVE HEART FAILURE

Waldman, S., and Pelner, L.: "Mercurial Fastness" in Patients with Congestive Heart Failure: Correction of this State by the Addition of Pyridoxine. Am. J. M. Sc. **225:** 39 (Jan.), 1953.

The failure of patients with chronic congestive failure to respond to mercurial diuretics after prolonged administration has led to administering the mercurial with various "extenders" such as ascorbic acid, aminophylline, and sodium dehydrocholate. Mercurial-resistant patients, no longer responding

to these combinations, were given injections of mercuhydrin, 2 cc. and pyridoxine, 100 mg., by intravenous or intramuscular routes. Ten such patients were found to have a satisfactory diuresis when treated with the mercuhydrin-pyridoxine mixture. The authors state that the mechanism of the action of pyridoxine in breaking "mercurial-fastness" is unknown but suggest that it is probably effective at an enzymatic level.

SHUMAN

CORONARY ARTERY DISEASE

Russek, H. I., and Zohman, B. L.: Anticoagulant Therapy in Acute Myocardial Infarction. A Survey of Specialists' Opinions Concerning Indications, Results and Dangers. Am. J. M. Sc. **225:** 8 (Jan.), 1953.

The authors surveyed the opinions of several hundred medical specialists by means of a questionnaire in an effort to determine their concepts of the indications for anticoagulant therapy, the drugs used, selection of patients for such treatment and their experience with hemorrhage as a result of the use of these drugs. It was found that most of the 228 physicians replying did not employ anticoagulant therapy routinely in treatment of myocardial infarction. Among the criteria determining the use of these drugs were previous infarction, congestive failure, large infarction, shock, severe pain, cardiac enlargement, arrythmias, varicosities and thromboembolic phenomena. Some regarded old age as an indication, others as a contraindication. Serious hemorrhagic complications were encountered by 45.6 per cent of the physicians; there were 122 deaths reported. About one-third of the physicians used heparin in conjunction with Dicumarol; the remainder did not use it at all or only in serious cases. It was decided that anticoagulant therapy is an important factor in the management of myocardial infarction but that routine use of these drugs is not desirable.

SHUMAN

Rubler, S., and Angrist, A. A.: A Study of Mural Thrombi in Myocardial Infarction as a Source of Embolization. Am. J. M. Sc. **225:** 20 (Jan.), 1953.

A survey of the records of autopsied patients with myocardial infarction and ventricular mural thrombi was made to determine the frequency with which the latter served as a source of embolization. Of 667 cases of myocardial infarction, 189 or 28.3 per cent had mural thrombi in one or both ventricles. These thrombi were the probable sources of 6 per cent of emboli noted in 46 patients. The location of the mural thrombus in 23 cases was the interventricular septum, and in 27 cases the apex of the left ventricle. The most common sites for embolization were the kidneys (37 instances) and the spleen (18). Left auricular thrombi in five, and thrombotic nonbacterial endocarditis in three cases were the sources of emboli. Ventricular aneurysms were the site of thrombi in 11 instances of embolization. Pulmonary infarction may have occurred from a right ventricular thrombus in one case; however, the majority of these emboli arose from thromboses of leg veins. Many so-called embolic occlusions may actually be thrombosis due to stasis within the vessel; 50 cases of thrombotic occlusions of arteries other than the coronaries were noted. The authors conclude that mural thrombi represent a significant source for embolization in myocardial infarction.

SHUMAN

Swan, H. R., and Simoson, L. H.: Hiccups Complicating Myocardial Infarction. New England J. Med. **247:** 726 (Nov. 6), 1952.

Two patients with acute myocardial infarction complicated by severe, protracted hiccuping are described. In both patients bilateral phrenic-nerve crush was performed in stages, after more conservative measures, including large doses of quinidine, failed. Both patients survived and were able to return to work. Neither patient experienced any respiratory embarrassment. Three other cases of hiccups complicating myocardial infarction are mentioned. These three patients died. Adequate treatment for this complication is said to include relief of gastric distention, adequate doses of quinidine until hiccups stop or signs of toxicity appear, and, if hiccups persist, fluoroscopic study to ensure that both leaves of the diaphragm are involved, in which case bilateral phrenic-nerve crush should be performed. The opinion is expressed that hiccups in coronary-artery disease are reflex in origin.

ROSENBAUM

Gilchrist, E., and Tulloch, J. A.: Observations on the Plasma Fibrinogen Content after Myocardial Infarction. Edinburgh M. J. **59:** 561 (Nov.), 1952.

An increase in plasma fibrinogen content occurs after myocardial infarction. The maximum increase is detected about one week after the acute episode, and is succeeded by a gradual fall in plasma fibrinogen levels. In one-third of all cases, the level has returned to within normal limits by the sixth week after the onset, but in the remaining two-thirds, the readings are still abnormal at this time. Plasma fibrinogen estimation may therefore be an additional aid in establishing in retrospect the diagnosis of coronary thrombosis. In some cases the levels may remain abnormally high three months after the acute incident. The more severe cases tend to show the greatest rise in plasma fibrinogen, and in these a longer time elapses before a normal level is restored. Patients observed from the onset react similarly whether treated conservatively or with anticoagulants. Patients first treated with anticoagulant therapy from the eighth day after the

attack, or later, show a further rise in plasma fibrinogen content from an already abnormally high level. This may be related to Tromexan administration.

BERNSTEIN

Wroblewsky, F., and LaDue, J. S.: Myocardial Infarction as a Postoperative Complication of Major Surgery. J. A. M. A. **150:** 1212 (Nov. 22) 1952.

A review of the clinical and autopsy data on 15 patients who had electrocardiograms showing unequivocal evidence of acute myocardial infarction following major surgical procedures is presented. The incidence of coronary occlusion following operation seems to be well under 0.8 per cent of the surgical cases in the hospital concerned. Ages of the patients ranged from 43 to 78 years with an average of 62 years. There were 11 men and 4 women. The incidence of hypertension in this group was 53 per cent as compared with 71 per cent and 74 per cent reported in the literature. Cardiac hypertrophy was encountered in only 23 per cent compared with the general incidence of 34 to 60 per cent. Chest pain occurred in only 27 per cent of these patients in contrast to the 97 per cent incidence of pain generally reported. The authors feel that several factors play a role in such infarctions; among these are (1) preexisting coronary artery disease, (2) blood coagulability, (3) surgical shock and anoxia, (4) blood volume alterations, and (5) tachycardia and/or arrhythmia. Anemia, type of anesthesia, and administration of parenteral fluids or blood did not appear to be correlated with the onset of these cases. The onset of the infarction occurred within three days postoperatively in 60 per cent of the patients, and 40 per cent of them succumbed. Coronary artery occlusion postoperatively can possibly be prevented if surgical or hemorrhagic shock is avoided, anoxia prevented, operative time minimized, and noncardiovascular complications prevented or controlled. Although only two of the patients here reported had a preoperative history of healed myocardial infarction, it is felt that patients with healed myocardial infarctions subjected to major surgery are more likely to have fresh ones postoperatively than are other patients of the same age group.

KITCHELL

ELECTROCARDIOGRAPHY

Hegglin, R.: The Problem of Disturbance of Metabolism of the Myocardium and the Electrocardiogram. Verhandl. deutsch. Gesellsch. Kreislaufforsch. **18:** 145, 1952.

A disturbance of contractility of the heart is reflected in the electrocardiogram in two principal forms namely shortening or prolongation of the Q-T duration. Biochemical data obtained under such conditions suggest that the electrocardiographic alterations are related to the amount of adenosine triphosphate (ATP) present in the myocardium, or to interference with the action of an enzyme (adenosinetriphosphatase). Both these substances appear to be, in contrast to actomyosin, especially sensitive to various external and metabolic factors.

Shortening of the Q-T duration occurs clinically in hypoxemia and anoxemia, under the effect of digitalis, and in hypercalcemia; it can be produced experimentally by warming the heart or poisoning it with monoiodacetic acid. In all these conditions, with the exception of hypercalcemia, the amount of adenosine triphosphate in the myocardium is decreased. In hypercalcemia its amount is normal but an increase of activity of adenosinetriphosphatase can be demonstrated. Prolongation of the Q-T interval is seen commonly in conditions associated with a disturbance of the electrolyte balance (hypocalcemia and hypokalemia). Experimental evidence is available demonstrating under these circumstances a diminution of the adenosinetriphosphatase activity in the heart muscle.

The author concludes that shortening of the Q-T duration can be ascribed to a low content of adenosine triphosphate in the heart, in the presence of normal or increased activity of adenosinetriphosphatase. Prolongation of Q-T is due to diminution of activity of adenosinetriphosphatase in the presence of a normal or even increased amount of adenosine triphosphate in the heart muscle.

PICK

Mahoney, D. I., and Kennedy, J. V.: Electrocardiographic Studies on Human Subjects Breathing Oxygen at Extremely High Pressures. J. Aviation Med. **23:** 560 (Dec.), 1952.

Four human subjects were used to study electrocardiographic change during balanced and unbalanced pressure breathing. The electrocardiograms indicate no alarming changes in the electrical activity of the heart during balanced and unbalanced pressure breathing at ground level, and balanced pressure breathing at 65,000 feet.

BERNSTEIN

Peyor, W. W., Sieker, H. O., and McWhorter, R. L.: Spatial Vector Analysis of the Electrocardiogram during Exposure to Positive Acceleration. J. Aviation Med. **23:** 550 (Dec.), 1952.

Standard limb and unipolar precordial lead electrocardiograms have been recorded simultaneously on seven healthy males during positive acceleration. The records were analyzed by the method of spatial vector analysis in an effort to separate changes in the electrical activity of the myocardium. At levels of acceleration insufficient to cause visual symptoms only one subject demonstrated alterations in the electrocardiogram described by earlier investigators. This subject was also the only one showing changes after being tilted to 90 degrees.

Among the remaining subjects only two showed any Tw changes, even when the acceleration was sufficient to cause "blackout." In these two instances the alterations in the Tw waves are less marked, but also are most likely secondary to changes in autonomic tone and filling of the heart. There was no S-T segment shift to suggest coronary insufficiency in any subject.

BERNSTEIN

Bayer, O., and Effert, S.: The Spatial Position of R and T Vectors in Mitral Valvular Lesions and Their Relationship to Pressure Conditions in the Pulmonary Circulation. Verhandl. deutsch. Gesellsch. Kreislaufforsch. **18:** 179, 1952.

In 35 cases of pure mitral stenosis and in 18 cases of combined mitral lesions hemodynamic findings determined by cardiac catheterization were correlated with the spatial direction of the mean QRS and T vectors. The authors came to the following conclusions: In mitral stenosis with marked pulmonary hypertension and diminution of left ventricular output the QRS vector usually points forward and to the right while the T vector has an upwards and backwards direction. This "discordance" of the two vectors was not found in mitral stenosis of slight degree or in mitral insufficiency. If some discordance of vectors was found in the latter condition, it was due to a rotation of the T vector while the QRS vector remained in its normal spatial position. In a case of mitral stenosis submitted to commissurotomy, both QRS and T vectors rotated back towards normal following surgery. This is ascribed to alleviation of the pulmonary hypertension and improvement of left ventricular filling which could be demonstrated in a re-examination following the operation.

PICK

Lipsett, M. B., and Zinn, W. J.: Anatomic and Electrocardiographic Correlation in Combined Ventricular Hypertrophy. Am. Heart J. **45:** 86 (Jan.), 1953.

The precordial and augmented limb leads of 73 electrocardiograms from patients with necropsy evidence of combined ventricular hypertrophy were analyzed. The right ventricular wall was at least 5 mm. in thickness, and the left ventricular wall at least 14 mm. in thickness. A group of 17 cases with a right ventricular wall measuring 3.5 to 4 mm. in thickness and a left ventricular wall 14 mm. or greater constituted the control group. On a necropsy basis, four groups evolved: (A) the control group, consisting of 17 cases of left ventricular hypertrophy in which the diagnosis of hypertensive heart disease had been made; (B) 46 cases of combined ventricular hypertrophy in which the etiology was hypertensive heart disease; (C) 9 cases of cor pulmonale and left ventricular hypertrophy; and (D) 18 cases of mixed valvular disease, mitral stenosis, and hypertension, including one case of ventricular septal defect. The electrocardiographic data were assessed against the criteria of Sokolow and Lyon.

When left ventricular hypertrophy occurred as a result of hypertensive or aortic disease, its recognition was slightly impaired by the concomitant right ventricular hypertrophy. Left ventricular hypertrophy associated with cor pulmonale was hidden electrocardiographically. Right ventricular hypertrophy occurring as a result of hypertensive heart disease or mitral disease was masked by the concomitant left ventricular hypertrophy. Cor pulmonale occurring with left ventricular hypertrophy was apparent. The electrocardiographic diagnosis of right ventricular hypertrophy in the presence of left ventricular hypertrophy may be suspected when atypical electrical positions are present, or the transition zone is shifted to the left.

In summary, the diagnosis of combined ventricular hypertrophy was difficult and apparent only in 10 cases of 73. In these cases, right ventricular hypertrophy was recognized by the rotational changes.

RINZLER

Ayala y de Landero, C.: A Simple Method to Obtain an Approximate Vectorcardiogram with an Ordinary Electrocardiograph. Frontal and Horizontal Planes. Am. Heart J. **45:** 60 (Jan.), 1953.

A simple method for obtaining an approximate vectorcardiogram by applying the commonly used leads of the electrocardiogram is presented. This method is applicable only to frontal and horizontal planes. For each plane the direction and magnitude of the instantaneous vectors are derived from suggested formulae and tables. Then, after obtaining a chosen number of instantaneous vectors, their ends can be joined by a line to form a vectorcardiogram. An alternative procedure is offered which consists of a diagram of graduated radii separated from each other by angles of 5 degrees, crossed by a series of concentric circles, the distance of these concentric circles from one another being 0.5 cm. By placing a sheet of copy paper on the diagram, ends of instantaneous vectors will be obtained. The graduated radii will indicate the direction, and the concentric circles the magnitude.

RINZLER

Gibert-Queralto, J., Torner-Soler, M., Paravasini, J., and Morato-Portell, J. M.: The Physiogenesis of the Left Intracavitary Electrogram. Verhandl. deutsch. Gesellsch. Kreislaufforsch. **18:** 84, 1952.

The authors report intracavitary and intravascular electrocardiograms obtained in man by retrograde catheterization (via the radial artery) of the left heart and aorta. There were no fatalities, but in one instance the procedure had to be interrupted because of development of ventricular tachycardia.

Left atrial potentials usually consist of an RS complex and thus resemble those obtained from the right atrial cavity. Their duration is 0.12 to 0.16 second and the relative size of the two waves depends on the position of the catheter. The left ventricular cavity potential is usually a QS deflection followed by an inverted T wave. A small R wave is sometimes seen following the large initial deflection and is considered by the authors to be part of an injury current when the catheter is in contact with the ventricular wall. Another possibility is that it is a reflection of the activation of a papillary muscle. Transient inversion of the T wave (to an upright wave) was observed following premature beats, sometimes in the form of an irregular alternans. The potential in the ascending aorta is a QRs or rS with positive or negative T waves, and in the descending aorta a Qr or qR followed by a negative T wave. The contour of the aortic leads depends on the position of the catheter tip relative to the posterior wall of the heart. Tracings from the descending aorta are, according to the authors, superior to esophageal leads.

PICK

Senning, A.: Electrocardiographic Studies of Cardiac Fibrillation during Artificial Perfusion. Verhandl. deutsch. Gesellsch. Kreislaufforsch. **18:** 97, 1952.

Using an artificial heart and lung of their own design, the authors were able to perform on dogs intracardiac operations of more than one hour duration. In the course of these experiments, during which the heart and the lungs were excluded from the circulation with exception of the blood supply to the coronary and bronchial arteries, ventricular fibrillation was induced by electric stimulation in order to stop the coordinated heart beat and thus to prevent air embolization. Onset and perpetuation of ventricular fibrillation during artificially maintained circulation is different from that seen ordinarily in animals in which circulation ceases with the onset of uncoordinated heart action. The electrocardiogram revealed that the rate of undulations did not exceed 700 per minute, and their size remained large until fibrillation was stopped by an induction shock or by Novocain. During the entire time of fibrillation the heart maintained its tone and mechanical undulatory activity remained visible.

PICK

Prestera, O. A., De Soldati, L., and Rabenko, J.: A Study by the Paracardiac Chest Leads in 1500 Clinical Cases. Rev. argent. cardiol. **19:** 436 (Nov.-Dec.), 1952.

Special chest leads had been previously described by Prestera. They differ from the V-leads because the central terminal is made by connecting the points 1, 3 and 5 of the precordium. The leads from 1, 3 or 5 to this terminal are called dC1, dC3, and dC5. It is to be noted that the leads are actually "augmented" leads because each wire is alternatively used either for the exploring electrode or as part of the central terminal. The authors' study is based on the tracings obtained by means of these electrocardiographic leads in 1500 clinical cases. Out of 468 normal subjects with normal electrocardiogram, 68 showed abnormalities in the new chest leads. Out of 418 hypertensive patients, the classic electrocardiogram was normal in 66.5 per cent while the new chest leads were normal only in 18.3 per cent. Out of 92 patients with angina pectoris, 34.7 per cent had electrocardiographic abnormalities in the classic leads while 82.6 per cent had abnormal findings in the new chest leads. These new leads seem, therefore, to increase the diagnostic utility of the electrocardiograph.

LUISADA

Alzamora-Castro, V., Abugattas, R., Rubio, C., Bouroncle, J., Zapata, C., Battilana, G., Binder, T., Santa Maria, E., Subiria, R., Paredes, D., and Pando, B.: Experimental Study of the Electrocardiographic Manifestations Accompanying Progressive Damage of the Cardiac Fiber. Rev. peruana cardiol. **1:** 229 (Oct., Nov., Dec.), 1952.

In 45 experiments, the authors injected a 2.5 or 5 per cent solution of cocaine into a coronary artery of the dog and studied the electrocardiographic manifestations produced by the damage of cardiac fibers. The changes were similar to those occurring after ligation of a coronary artery. Minimal damage produced a delay in the recovery process, for instance, primary T-wave changes. Variations in the form and duration of the QRS complexes occurred when the damage was more pronounced. Monophasic curves appeared with severe damage. Injury currents, always present in muscular damage caused by ischemia, may or may not be part of the electrocardiographic manifestations caused by cocaine injection. The nonspecific electrocardiographic manifestations produced by damage to the cardiac fibers are described as "fiber blocks" by Alzamora-Castro and co-workers.

LUISADA

Carlotti, J., Capretti, G., and Joly, F.: Electrocardiographic Study in 39 Cases of Isolated Intracardiac Communications. Arch. mal. coeur **45:** 1121 (Dec.), 1952.

Electrocardiographic findings are reported in 16 cases with isolated auricular septal defects, in 17 cases with ventricular defect, and in 6 cases of Eisenmenger's complex.

In auricular septal defects there is frequently right axis deviation and a relatively frequent prolongation of A-V and intraventricular conduction time. However, a typical pattern of right bundle branch block was found in only 3 of the 16 cases. Roger's disease does not modify the electrocardio-

gram, but in large interventricular communications with enlargement of the pulmonary artery the tracings become similar to those seen with atrial septal defects. In interventricular septal defects associated with aortic regurgitation the pattern of combined heart strain may be found. In Eisenmenger's complex the only constant electrocardiographic finding is right heart strain, sometimes associated with large and diphasic QRS complexes in the standard leads.

In contrast to conditions present in various types of pulmonic stenosis, no correlation could be established in isolated septal defects between electrocardiographic findings and hemodynamic data. The authors, therefore, conclude that the electrocardiogram is of little value in the differential diagnosis of various types of isolated intracardiac communications.

PICK

Lutembacher, R.: The Electrogram of the Auricle. Arch. mal. coeur **45**: 1099 (Dec.), 1952.

The author studied the characteristics of auricular potentials with direct bipolar leads from the auricle of the frog heart. Activation of the auricular wall is indicated by a rapid initial deflection, the P wave. A subsequent slow deflection (t) may be masked by simultaneous occurrence of t deflections of opposite direction at the two ends of auricular fibers. If, however, one auricular pole is warmed or cooled, this equilibrium is disturbed and a positive or negative t wave becomes manifest. Following compression of the A-V region, resection of the ventricles or cauterization of the lower part of the auricle the Pt complex becomes monophasic and dome-shaped. A similar change of opposite direction takes place following cauterization of the upper portion of the auricle. The duration of the t wave can be prolonged by cooling or shortened by warming or application of calcium chloride or digitalis. Thus the electrical manifestations of activation and deactivation of the auricles are similar to those of the ventricles. The rapid initial deflection corresponds to the rapid twitch of shortening of the muscle fiber, and the t wave to its persistence in contraction. In voluntary muscle the second part of electrical activity does not occur unless the muscle is veratrinized and remains in contraction following stimulation.

PICK

Elek, S. R., Silver, A. S., Tober, J. N., and Griffith, G. C.: The Q-T Interval in Myocardial Infarction and Left Ventricular Hypertrophy. Am. Heart J. **45**: 80 (Jan.), 1953.

By use of semilogarithmic plotting, the Q-T formula of Ashman was simplified and reduced to a straight line. Then the Q-T interval was measured in 86 cases of acute myocardial infarction and 140 cases of left ventricular "strain" and hypertrophy. Lead II was usually used and the average value of at least five consecutive complexes were taken. No significant prolongation was found in 120 cases of left ventricular hypertrophy. In the 86 cases of acute myocardial infarction, the Q-T interval was significantly prolonged. No reduction in this interval occurred during the first few weeks after myocardial infarction.

RINZLER

Dussaillant, G., Lepe, A., and Gómez, G.: Clinical Experience with EKY. II: Valvular Lesions and Congenital Heart Diseases. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19**: 238, 1952.

In mitral insufficiency, both functional and organic, a systolic distension in the electrokymogram (EKY) of the left auricle was observed. This is due to regurgitation. In another series of observations, the electrokymogram of the pulmonary veins revealed a similar finding. Isolated observations of auricular electrokymograms of normal subjects can show equivocal patterns. However, multiple tracings reveal that the abnormal pattern is due to artefacts. Therefore, the auricle should be studied at various points and in various projections. Suggestive changes have been observed in cases of mitral stenosis, but their evaluation requires further studies.

The steep characteristics of the aortic electrokymogram are suggestive, but nondiagnostic, of aortic insufficiency because similar tracings have been observed in normal subjects (predominance of motion over volume changes). However, the characteristic syndrome is composed of a steep aortic pulse, a large aortic pulse (over twice that of the pulmonary artery), a premature and rapid diastolic expansion of the left ventricle, an early onset and an abnormal prolongation of the ejection. The right auricular tracings were of doubtful value in tricuspidal insufficiency. On the other hand, large, positive, systolic waves of the vena cava and diaphragm (hepatic pulse) were found to be characteristic. In two cases of tricuspid stenosis, large presystolic (auricular) waves were found in the tracings of the vena cava, the diaphragm, and the right auricle.

Pulmonary insufficiency seems to be characterized by steep pulses in the electrokymographic tracings of the pulmonary artery, large amplitude of these pulsations as well as those of the hila and pulmonary fields, and early ejection of the right ventricle. A limited experience with cases of auricular defects has shown changes resembling those of pulmonary insufficiency except for the absence of an early right ventricular emptying.

The results in cases of patent ductus arteriosus were to some extent similar to those observed in aortic insufficiency. These changes disappeared after surgical correction.

LUISADA

Barrera, F., Abi-Caram, C., and Bustamante, R.: EKY Studies of the Medial Arch of the Cardiac Silhouette in Normal Subjects and in Patients with Mitral Stenosis. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19**: 239, 1952.

The electrokymogram of the medial arch of the cardiac silhouette in normal subjects and in patients with mitral stenosis was studied in the frontal, 10 degrees left anterior oblique, and 10 degrees right anterior oblique positions. Tracings obtained in the lower part of the medial arch suggested that the left auricular appendage formed part of the silhouette in over one-half of normal subjects, and in a variable proportion of patients with mitral stenosis. The latter was observed in cases where neither radiography nor angiocardiography had given such indication. This observation seems to be confirmed by roentgenographic studies in patients with mitral stenosis who had been subjected to commissurotomy and excision of the left auricular appendage.

LUISADA

Zapata, J., and de León, L. D.: ECG Changes During Experimental and Clinical Pulmonary Edema. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19**: 276, 1952.

Acute pulmonary edema was induced in 16 dogs by rapidly injecting 1,000 cc. of normal saline into the distal ends of both carotid arteries. In all experiments, simultaneous electrocardiograms in the standard limb leads, in the chest leads, and in the cavitary leads were recorded. In some experiments, the arterial and left ventricular pressures were also recorded. Autopsies were performed in all but one dog in order to ascertain existence and severity of the edema.

During the infusions, the following changes were observed: sinus bradycardia, sinus arrhythmia, first and second degree A-V block, S-A block, and occasional premature contractions. The P wave showed a decreased voltage in all leads; the QRS presented decreased S-waves in the leads recording left ventricular potentials (levorotation). Changes of S-T and T of a variable degree and of a short duration were observed. They consisted of T changes suggestive of subendocardial ischemia, or S-T and T changes suggesting injury and ischemia of the left ventricle. They were transitory and disappeared within a few seconds of the end of the infusion. Dogs presenting pulmonary edema showed similar S-T changes, but more accentuated and more permanent. Evidence of injury and of subendocardial ischemia appeared simultaneously with the clinical signs of edema. Two dogs had also evidence of right ventricular injury and ischemia.

The various possible mechanisms causing the above electrocardiographic changes are considered. Clinical tracings of cases with various cardiac diseases, during and after episodes of acute pulmonary edema, are also presented and discussed. Similarities between the electrocardiographic changes produced by experimental and by clinical pulmonary edema are pointed out, in spite of the different mechanism.

LUISADA

HYPERTENSION

Taylor, R. D., Dustan, H. P., Corcoran, A. C., and Page, I. H.: Evaluation of 1-Hydrazinophthalazine ("Apresoline") in Treatment of Hypertensive Disease. Arch. Int. Med. **90**: 734 (Dec.), 1952.

Ninety-seven patients with hypertensive disease of widely varying severity and clinical classification were treated with Apresoline as the only antipressor drug; a quarter of the group responded by decreases of diastolic pressure to normal and a third by decreases to pressure of less than 110 mm. Hg. Thus, more than one-half responded favorably. The relatively high incidence of good responses in patients whose hypertension could be presumed to be predominantly neurogenic accords with the concept that the drug may act specifically on a pathogenic cerebral humoral pressor mechanism.

Pre- and post-treatment clinical status were summarized as a numerical severity index. Among the factors other than arterial pressure which entered into the index, those reflecting cerebrovascular disease showed the most improvement. In the renal panel there occurred remissions of progress of nephrosclerosis and, sometimes, increases in renal function. The average cardiac status of the group who otherwise responded favorably showed little improvement, although some patients obtained substantial relief of hypertensive heart disease. Deteriorations of cardiac status were not uncommon in patients of older age groups; they are attributable to the effects of the drug on the rate and output of the heart and the limitations imposed by tachycardia and coronary atherosclerosis. Consequently, for older patients, the aim should be to maintain diastolic pressure at about 100 mm. Hg. For patients with severe hypertensive heart disease, sodium restriction and digitalization are suggested as adjuncts to treatment with Apresoline.

BERNSTEIN

Dustan, H. P., Mason, H. L., and Corcoran, A. C.: Urinary Formaldehydogenic Corticoid as Determined after Enzymatic Hydrolysis in Normal Subjects and in Patients with Adrenal and Hypertensive Disease. J. Clin. Investigation **32**: 60 (Jan.), 1953.

Corticosteroids appear in the urine in a free form and as conjugates. Treatment of the urine with spleen β-glucuronidase causes an increase in the yield of both reducing and formaldehydogenic corticoids because of the hydrolysis of the bound corticoid as glucuronide. In a group of 35 patients with essential hypertension, 80 determinations on 24-

hour urine samples showed that the level of free formaldehydogenic corticoids was often increased and widely variable; however, by use of the β-glucuronidase it appears that the outputs of total corticoids are not increased, and the increased outputs of the free form sometimes observed are associated with a decrease in the ratio of total to free corticoid. This may result either from some defect in corticoid conjugation or from intrarenal or intraurinary hydrolysis of preformed corticoid glucuronide.

WAIFE

Entwisle, G., and Stone, C. A.: Effect of Prolonged Administration of Adrenergic Blocking Drug on Blood Pressure of Hypertensive Dogs. Am. J. Physiol. **172:** 245 (Jan.), 1953.

An aryl-haloalkylamine adrenergic blocking drug, N-ethyl-N-(2 chlorethyl)-9-fluorenamine-HCl, produced a small but significant reduction in the blood pressure of Goldblatt renal hypertensive dogs when given by mouth in doses of 5 mg. per kilogram twice daily for two weeks. Although blocking to ephinephrine lasted only six to eight days after the drug was discontinued, the low arterial pressure lasted two to four weeks. It is suggested that the decrease in pressure may be related to a change in adrenal cortical function rather than to block of adrenergic nerves.

OPPENHEIMER

Danford, H. G., and Herrin, R. C.: Adrenal NaCl and Experimental Hypertension. Am. J. Physiol. **171:** 412 (Nov.), 1952.

The kidneys of rats were wrapped with silk. Those which became hypertensive showed a greater reduction in lymphocytes than those which remained normotensive after the operation. Although restriction of calories or administration of pyroxidine lowered the number of lymphocytes in hypertensive rats, there was no effect on blood pressure. If salt deficiency has its hypotensive effect by way of the adrenals, the authors suggest that it is a specific factor. Sodium chloride produced a pressor response in rats whose hypertension had been previously reduced by salt restriction. Cortical extract was effective in similar rats.

OPPENHEIMER

PATHOLOGIC PHYSIOLOGY

Berson, S. A., Yallow, R. S., Post, J., Wisham, L. H., Newerly, K. N., Villazon, M. J., and Vazques, O. N.: Distribution and Fate of Intravenously Administered Modified Human Globin and Its Effect on Blood Volume. Studies Utilizing I^{131} Tagged Globin. J. Clin. Investigation **32:** 22 (Jan.), 1953.

Globin derived from human red blood cells has been suggested as a plasma expander. In this study modified human globin was iodinated with I^{131} and administered to patients receiving Lugol's solution (five drops three times a day during the studies), which was effective in inhibiting thyroid uptake of of I^{131}. The studies suggest that globin is rapidly removed from plasma by the liver and by passage through capillaries throughout the body. The rate of disappearance was inversely related to the quantity administered. Even at the highest loads, however, approximately one-half to two-thirds of the globin had left the plasma at the conclusion of the infusion. About 10 per cent was excreted as such in the urine; the major portion was rapidly metabolized. A comparative study of the rates of disappearance of this material infers that the capillary wall is much more permeable to globin than to albumin.

The plasma volume changes were slight and transient following intravenous globin when compared with similar doses of human serum albumin. These studies do not establish the clinical usefulness of globin as a plasma expander.

WAIFE

Bayer, O., Wolter, H. H., Teige, I., and Rippert, R.: The Calculation of Openings of Stenosed Valves Demonstrated in Cases of Mitral and Pulmonary Stenosis. Ztschr. Kreislaufforsch. **41:** 926 (Dec.), 1952.

In 20 cases with mitral stenosis and in six cases with congenital pulmonary valvular stenosis the size of the valve ostium was calculated according to the formulas of Gorlin and correlated with clinical, surgical and postmortem findings. In cases with mitral disease the calculated valve orifice was between 0.6 and 2.8 sq. cm. A control in 12 cases on the operating or autopsy table revealed close agreement with actual measurements with the exception of two cases who had mitral regurgitation. The estimated difference, however was not more than 0.2 sq. cm. The degree of clinical symptoms and signs was clearly dependent upon the valvular size. Mitral surgery is, according to the authors, indicated with a mitral ostium of less than 1.5 sq. cm. and especially below a critical value of 1.0 sq. cm. In the six cases of valvular pulmonary stenosis, the opening was calculated as being between 0.4 and 1.8 sq. cm. Here the authors consider Brock's operation proper when the valvular opening is less than 0.8 sq. cm.

PICK

Biörck, G., Axén, O., Krook, H., Andrén, L., and Wulff, H. B.: Studies in Mitral Stenosis. IV. The Relative Merits of Various Diagnostic Methods in Mitral Valvular Disease. Am. Heart J. **45:** 13 (Jan.), 1953.

The following methods were employed to determine which diagnostic signs were most useful for the evaluation of mitral regurgitation in a number of candidates for mitral valvulotomy who had mitral valvular disease: palpation of the apex beat, auscul-

tation, standard and unipolar electrocardiography, electrokymography, roentgenography of the heart, angiocardiography, cardiac catheterization, ballistocardiography and determinations of the circulation rate. This series of tests gave information regarding left ventricular size, murmurs at the mitral orifice, pressure and volume changes in the left auricle and the pulmonary veins, and the passage of blood through the lesser circulation and the left heart. When the preoperative conclusions as to preponderance of mitral stenosis and mitral regurgitation by the above described methods were compared with the surgeon's impression at operation, the greatest degree of verification was arrived at in the following order: (1) auscultation, (2) heart roentgenography, (3) angiocardiography and electrokymography, (4) unipolar chest lead electrocardiogram, (5) apex beat, (6) determinations of electric axis in the standard electrocardiogram, and (7) pcv tracings at cardiac catherization.

RINZLER

Cathcart, R. T., Field, W. W., and Richards, D. W., Jr.: Comparison of Cardiac Output Determined by the Ballistocardiograph (Nickerson Apparatus) and by the Direct Fick Method. J. Clin. Investigation **32:** 5 (Jan.), 1953.

By use of the direct Fick (cardiac catheterization) technic, the cardiac output was measured in 40 individuals and compared with the Nickerson critically damped ballistocardiograph. Sixty-four determinations were performed in this group which consisted of both normal and miscellaneous patients from the general ward population. Because apnea alters the ballistocardiographic record in an unpredictable manner, the ballistocardiograms were taken during quiet breathing. Respiratory overactivity distorted the records of about 40 per cent of hospital patients, especially those with cardiac or pulmonary disease.

There was a wide scatter and a poor correlation in the comparison of cardiac outputs by these two methods both under basal metabolic conditions and during the intravenous infusion of epinephrine. Thus, the average cardiac output in the group calculated by the direct Fick method was 6.23 liters per minute as compared with an average ballistocardiographic output of 4.49 liters a minute. Even with application of an arbitrary correction factor to bring the average ballistocardiographic reading closer to the Fick reading, there were marked discrepancies in a large proportion of instances. The authors feel that this type of ballistocardiograph does not provide an accurate method for measuring cardiac output.

WAIFE

Zanetti, M. E.: Significance of Elevated Portal Vein Pressure in Etiology of Hemorrhagic Shock. Am. J. Physiol. **171:** 538 (Dec.), 1952.

These experiments demonstrate that portal vein pressure may be elevated after hemorrhage and reinfusion even though circulatory failure does not follow. This situation was present in 6 of 14 dogs after acute hypotension and in three of six dogs after a longer period of hypotension. None of these animals progressed into hemorrhagic shock. One animal developed irreversible shock in the absence of any rise in portal pressure. Thus, postinfusion-elevated portal pressure may be found to follow acute or prolonged hemorrhagic treatment which does not lead to circulatory failure as well as drastic hypotension which does induce irreversible shock. The author concludes that, although elevated portal pressure may be present in irreversible hemorrhagic shock, it cannot be considered a primary irritating factor in the development of this condition.

OPPENHEIMER

Delle Vedove, A.: Eosinophilia in Digitalized Cardiac Patients. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19:** 398, 1952.

The author studies the effect of digitalis upon the number of eosinophils in the peripheral blood. Patients with right heart failure were selected. Eosinophil counts were made before and after administration of digitalis.

The effect of intravenous atropine upon the eosinophil count of digitalized patients was also studied after suspension of the administration of digitalis. Eosinophil counts were made before digitalis suspension, one hour and 24 hours after administration of atropine. The same study was repeated in normal subjects.

The causes of eosinophilia are discussed and a critical evaluation of the problem is made. The most likely causes for the changes in the eosinophil counts of normal subjects and cardiac patients following digitalis or atropine are analyzed.

LUISADA

Arthur, H. R., and Chalmers, J. D.: Post-Partum Blood Pressure Levels. Edinburgh M. J. **59:** 555 (Nov.), 1952.

Two thousand and one records of delivery were examined for blood pressure recordings immediately after labor. One thousand seven hundred and fifty-eight were found to be within normal limits and 243 (12.3 per cent) to be raised. Of the 243 cases in the hypertensive group, 126 were found to have evidence of antepartum hypertension, 11 had incomplete records and 106 (43.6 per cent) had no evidence of any raise in blood pressure either in pregnancy or at the beginning of labor. The 106 cases (5.3 per cent of the whole series) of unexpected postpartum hypertension were analyzed for the type of labor and for the general factors of age, parity and maturity. No common etiologic factors were found.

Follow-up of the cases showed that in the majority (at least 75 per cent) the hypertension had disap-

peared in two months without special treatment. A suggestion is made that this may be a manifestation of subclinical toxemia. In view of the occasional occurrence of postpartum eclampsia and hypertensive cardiac failure, it is suggested that the result of the investigation justifies and necessitates routine recording of the blood pressure at the end of labor.

BERNSTEIN

Zoll, P. M.: Resuscitation of the Heart in Ventricular Standstill by External Electric Stimulation. New England J. Med. **247:** 768 (Nov. 13), 1952.

This report describes the use of a thyratron physiologic stimulator to generate periodic impulses of direct current. These were monophasic currents of low voltage, with rectangular shape, 2 to 20 milliseconds in duration and of variable intensity and frequency. The application of the instrument is described in two patients with coronary arteriosclerotic heart disease and ventricular standstill after complete heart block.

Subcutaneous needle electrodes were placed in the axillas at points in a line traversing the ventricles. In the first patient the heart was kept beating for 25 minutes before the patient died of cardiac tamponade due to prior repeated cardiac punctures. The heart was kept beating for five days in the second patient, being stimulated at intervals when cardiac standstill occurred or when there was a slow ineffective idioventricular rhythm. On one occasion the heart was kept beating for a period of 52 hours during which time not a single spontaneous ventricular beat was observed. The patient ultimately developed a spontaneous idioventricular rhythm and survived. The ventricular beats induced by the external electric stimulator were effective in maintaining an adequate blood pressure, cerebral and peripheral blood flow.

ROSENBAUM

Connolly, D. C., Tompkins, R. G., Lev, R., Kirklin, J. W., and Wood, E. H.: Pulmonary-Artery Wedge Pressures in Mitral Valve Disease; Relationship to Left Atrial Pressures. Proc. Staff. Meet., Mayo Clinic **28:** 72 (Feb.), 1953.

In patients studied by direct recordings of pressure at operation, tracings of pressure made when the catheter tip was wedged in a small pulmonary artery have been found to correlate closely both in pressure and in contour with recordings of left atrial pressures made simultaneously. The oxygen saturation of blood withdrawn from the catheter with the tip in the pulmonary artery wedge position usually exceeds the saturation of systemic arterial blood; this difference is exaggerated when low mixtures of oxygen are breathed. However, on occasion, venous blood can be obtained when the tip of the catheter is in the wedge position.

The recording of pressures with the catheter tip in the pulmonary artery wedge position has been free from complications in all the 181 patients from whom such tracings have been obtained. Satisfactory mitral commissurotomy usually is followed by an immediate decrease in left atrial and pulmonary artery pressure, of approximately the same magnitude. The contours of pulmonary artery wedge pressure cannot be considered an infallible index of the presence or absence of mitral insufficiency.

SIMON

Brasil, A.: Organic Sino-Auricular Depression. A New Disturbance of the Cardiac Rhythm. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19:** 331, 1952.

The author calls "organic sino-auricular depression" a stable cardiac rate, with normal rhythm, which is not due to the influence of drugs or to vagus stimulation. Little or no change in frequency is produced by exercise, changes in position of the body, emotion, effort, fever, heart failure, atropine; nor by digitalis, or oculocardiac or carotid reflexes. This depression was observed in Chagas' disease, but seems to exist in other cardiac diseases; it is recognized by administering 2 mg. of atropine intravenously and observing possible electrocardiographic changes.

The depression is attributed to the depressive effect of the toxin produced by *S. cruzi* upon the sino-auricular node. A specific action of this toxin seems to be suggested by the great frequency of blocks observed among patients with Chagas' disease, including young adults without previous evidence of myocarditis. Among 200 patients between 10 and 70 years of age, this disturbance was observed in 26 per cent of the cases (13.5 per cent with a heart rate between 50 and 75).

LUISADA

Hidalgo, J., Fowell, A. H., and Ralls, R. J.: Effect of Tissue Damage on the Plasma Fibrinogen Level. Surg., Gynec. & Obst. **95:** 661 (Dec.), 1952.

Rabbits were subjected either to a minimum of tissue injury or to a considerable degree of trauma, and the effect upon the fibrinogen level of the blood was determined. It was found that initially slight damage produced statistically insignificant reductions in fibrinogen concentration, while more extensive injury resulted in a significant decrease. Both types of trauma caused a definite increase in plasma fibrinogen concentration after 24 hours.

It is the opinion of the authors that the changes observed were due to the liberation of thromboplastin from injured tissues.

ABRAMSON

Araujo, J., and Lukas, D. S.: Interrelationships among Pulmonary "Capillary" Pressure, Blood Flow and Valve Size in Mitral Stenosis. The Limited Regulatory Effects of the Pulmonary

Vascular Resistance. J. Clin. Investigation. **31:** 1082 (Dec.), 1952.

Thirty-six patients with mitral stenosis of varying severity were studied by the cardiac catheterization technic. In patients with severe stenosis but not in failure, pulmonary capillary pressure at rest was fixed within the range of the plasma protein osmotic pressure. This was accomplished at the expense of the resting cardiac output, which in turn varied directly with the size of the mitral orifice. The mechanism by which a reduction in cardiac output, which is needed for regulation of the "capillary" pressure, is accomplished is not known. There was no correlation between the mitral valve size and the pulmonary vascular change. Large increases in this "capillary" pressure occur during exercise and were not prevented by an increase in the pulmonary vascular resistance; nor was there any evidence that arteriolar constriction occurred when the "capillary" pressure attained protein osmotic levels. Despite "capillary" pressures at or above such levels, alveolar edema was rarely detected. This suggests that changes in the alveolar membrane itself rather than in the pulmonary arterial tree protect against pulmonary edema, and the increased pulmonary vascular resistance in mitral stenosis is primarily the result of anatomic changes in the vessels.

WAIFE

Schieve, J. F., and Wilson, W. P.: The Changes in Cerebral Vascular Resistance of Man in Experimental Alkalosis and Acidosis. J. Clin. Investigation **32:** 33 (Jan.), 1953.

There is evidence that the cerebral vascular resistance in man is primarily under chemical control. The potent regulators are known to be anoxia, carbon dioxide retention, or a decrease in the pH of arterial blood. Patients convalescing from a variety of illness were studied by the nitrous oxide technic. Metabolic alkalosis was produced by the intravenous administration of 3 per cent sodium bicarbonate. Under these conditions the cerebral blood flow was increased to 65 per cent above resting normal values; isotonic bicarbonate solution (1.2 per cent) caused a 30 per cent increase. This change in blood flow was not due to changes in intravascular volume because an equivalent degree of hemodilution produced by isotonic saline did not increase the cerebral flow. Two per cent sodium chloride solution caused a smaller increase in blood flow than an equally hypertonic sodium bicarbonate solution. On the other hand, 0.8 per cent ammonium chloride solution reduced the blood flow approximately 20 to 25 per cent. These studies show that, in the absence of anoxia, the total carbon dioxide content of arterial blood more closely regulates cerebral vascular tone than the arterial pH levels; that is, when one compares the directional changes in total carbon dioxide content of arterial blood with those of the cerebral blood flow, there is a close correlation.

WAIFE

Cassels, D. E., and Morse, M.: The Arterial Blood Gases, the Oxygen Dissociation Curve, and the Acid-Base Balance in Polycythemia Vera. J. Clin. Investigation **32:** 52 (Jan.), 1953.

Patients with polycythemia vera were studied and compared with normals and with those with polycythemia secondary to congenital heart disease. It was found that 7 of 17 patients with polycythemia vera had arterial oxygen saturation levels below normal; furthermore, normal arterial saturation found in some patients with polycythemia vera, including those with the highest hemoglobin concentrations, leads to the conclusion that polycythemia itself is not the cause of the arterial oxygen unsaturation.

The oxygen dissociation of the blood was normal. This is in contrast to the shift to the right in secondary polycythemia, and indicates that this latter fact is not due to polycythemia alone and may be an important diagnostic aid. Breathing oxygen raises the oxygen content of arterial blood among polycythemia patients to a degree comparable to that in normal arterial blood, and this eliminates venous admixture as a cause of arterial unsaturation in polycythemia vera.

The results seem to show that, while the hemoglobin in the blood of polythemia vera is normal in respect to its oxygen binding and dissociation characteristics, the hemoglobin in the blood of polycythemic patients with cyanotic congenital heart disease is abnormal in these respects.

WAIFE

Winter, S. T., Ehrenfeld, E. N., and Feldman, J.: Total Drainage of Pulmonary Veins into the Right Atrium. Arch. Dis. Childhood **27:** 539 (Dec.), 1952

A case of drainage of all the pulmonary veins into the posterior wall of the right atrium is reported. Autopsy showed a transposition of all the pulmonary veins to the right atrium, a patent foramen ovale and a rudimentary left atrium, hypertrophy and enlargement of the right ventricle and right atrium, patent ductus arteriosus, and pulmonary atelectasis. The patient died at 10 weeks.

BERNSTEIN

PATHOLOGY

Portheine, H.: The Vector Diagram in Hypertrophy and Dilatation of the Left Ventricle. Verhandl. deutsch. Gesellsch. Kreislaufforsch. **18:** 196, 1952.

In 300 patients with clinical evidence for various degrees of left ventricular strain, direct vectorcardiograms were recorded according to the method of

Schellong using three thoracic leads each in the frontal and sagittal plane. The transformation of the normal QRS loop having a clockwise rotation into the abnormal contour with counterclockwise rotation, characteristic for left ventricular strain, takes place gradually and in a certain order. The first alteration is a torsion of the proximal portion of the loop, progressing towards its apex and associated with an augmentation of its "S" portion. The earliest stages of this characteristic alteration can be seen in the vectorcardiogram at a time when the conventional electrocardiogram is still within normal limits. The successive stages of alterations of vectorcardiogram can be correlated with the well known evolution of anatomic changes occurring in the left ventricle work-up under chronic strain.

PICK

Rodrigo, F. A.: Estimation of Valve Area and "Valvular Resistance." A Critical Study of the Physical Basis of the Methods Employed. Am. Heart J. **45:** 1 (Jan.), 1953.

Two methods of calculating the size of the opening of the valves have been offered to assist in the proper selection of patients for surgical correction of pulmonary and mitral stenosis. The formula of Gorlin and Gorlin allows for calculation of the valvular area. A second formula, based on Poiseuille's law, is intended to be used as an approximate estimate of the degree of stenosis by calculating "valvular" resistance. The author in comparing the merits of these formulae points out that the "constant" used by the Gorlins proves to be a variable term unless its use is limited to small orifices and a 10 per cent error allowed. As for the valve "resistance" formula, the author states it depends on the theory that blood may be considered as a liquid with a negligible viscosity in the valve opening. As the flow is not laminar, however, the formula for resistance becomes invalid, for, in applying the formula, the stenotic index is found to be directly proportional to the volume flow.

The empirical values for the constant of some defects, calculated by Gorlin and Gorlin, are compared with those obtained theoretically and are found to agree satisfactorily.

RINZLER

Reeves, R. L.: The Cause of Acute Pericarditis. Am. J. M. Sci. **225:** 34 (Jan.), 1953.

To evaluate the incidence of the various causes of acute pericarditis, the records of 129 patients on whom this diagnosis had been made over a 16-year period were reviewed. The criteria for diagnosis included autopsy proof, pericardicentesis, typical electrocardiographic alterations, roentgenographic findings, classic physical signs including friction rub, and history indicative of pericarditis. It is of interest that only 7 of 32 autopsied patients on whom electrocardiograms were obtained had electrographic findings indicative of pericarditis. The roentgenographic studies were consistent with the diagnosis in over half of the cases of tuberculous pericarditis but in only one-third of the other types. Pulmonary infiltrations were commonly encountered only in pyogenic pericarditis. Pericardial friction rub was present in 93 per cent of the rheumatic cases and in over 50 per cent of the other types of pericarditis. The leukocyte count was elevated in all cases except tuberculous pericarditis which was the highest in the pyogenic group. Omitting ischemic pericarditis, there were 96 cases of which rheumatic fever accounted for 40.6 per cent, purulent pericarditis 19.8 per cent, tuberculous pericarditis 7.3 per cent, benign nonspecific pericarditis 10.4 per cent, uremia 11.5 per cent, neoplasm 3.1 per cent, collagen disease 2.1 per cent. There were 5.2 per cent of the total for which no cause was ascertained.

SHUMAN

PHARMACOLOGY

Friedberg, C. K., Halpern, M., and Taymor, R.: The Effect of Intravenously Administered 6063, the Carbonic Anhydrase Inhibitor, 2-Acetylamino-1,3,4-thiadiazole-5-sulfonamide, on Fluid and Electrolytes in Normal Subjects and Patients with Congestive Heart Failure. J. Clin. Investigation. **31:** 1074 (Dec.), 1952.

Carbonic anhydrase is an enzyme present in the renal cortex as well as in other tissues; it has an important part in the acidification of the urine and reabsorption of sodium. The inhibition of carbonic anhydrase and the prevention of the formation of an acid urine may reduce abnormal sodium retention in congestive heart failure. A heterocyclic sulfonamide, which is 50 to 400 times more effective than sulfanilamide and nontoxic in effective doses, was administered to 15 subjects—3 controls and 12 with congestive heart failure of varied etiology. Metabolic studies during and following an infusion of this compound revealed that bicarbonate, sodium, and potassium excretion were markedly increased whereas chloride and phosphate excretion were increased only slightly. Ammonia excretion diminished. The increment in sodium excretion appeared to be related to the sodium intake in the days prior to the experiments and slightly, if at all, to the presence or absence of heart failure. There was a moderate increase in the excretion of water and a moderate weight loss in the 24 hours of the experiment despite the fact that cardiac patients had become free of edema previously or had been refractory to mercurial diuretics. There was no significant change in the plasma sodium and potassium following a single intravenous injection; however, intravenous 6063 following two days of oral 6063 led to acidosis with a blood bicarbonate value in the range of 15

mEq. per liter. Despite this acidosis there was a marked excretion of sodium and bicarbonate in an alkaline urine.

The authors postulate that bicarbonate reabsorption in the distal tubule depends on the hydrogen ion secretion, whereas reabsorption of the corresponding sodium ions could be accomplished by either hydrogen ion or potassium ion secretion. No toxic effects were observed, and the biochemical effects support the concept that carbonic anhydrase plays an important part in the conservation of base.

WAIFE

Berne, R. M., Hoffman, W. K., Jr., Kagan, A., and Levy, M. N.: Response of Normal and Denervated Kidney to L-Epinephrine and L-nor-epinephrine. Am. J. Physiol. **171:** 564 (Dec.), 1952.

In these experiments chronically denervated kidneys were more sensitive to epinephrine and norepinephrine than were normal controls. Both drugs had similar effects on normally innervated renal vessels as evaluated by reduced renal plasma flow, unchanged glomerular filtration rate and an increased filtration fraction. However, in the denervated kidney, renal plasma flow and glomerular filtration rate were lowered by both drugs in a proportionate fashion and as a result the filtration fraction was largely unchanged. Increase of efferent arteriolar resistance was equal in both types of kidney with epinephrine. On the other hand afferent and postarteriolar resistance was much more increased in denervated kidneys with epinephrine. It is suggested that in the denervated kidney epinephrine acts chiefly on the afferent arteriole. Norepinephrine produced a greater rise in afferent, efferent and postarteriolar resistance of the denervated kidney than did epinephrine. Both drugs increased tubular reabsorption of sodium even when tubular load was increased by increased gomerular filtration rate in both denervated and normally innervated kidneys. The authors point out that these drugs do not act via renal nerves.

OPPENHEIMER

Churney, L.: Effect of Epinephrine on Monophasic Action Potential of Auricular Muscle. Am. J. Physiol. **171:** 516 (Dec.), 1952.

Epinephrine does not change the monophasic auricular action potential. However, stimulation of the vagus decreases its amplitude and duration as well as accelerating the rate of fall of the repolarization limb. Epinephrine opposes both these effects and the negative inotropic action. Evidence is included to the effect that epinephrine acts directly on muscle and not by opposing release of acetylcholine at vagus endings in auricular muscle.

OPPENHEIMER

Greenman, L., Weigand, F. A., and Danowski, T. S.: Cation Exchange Resin Therapy in Patients Receiving Cortisone and ACTH. Am. J. M. Sc. **225:** 1 (Jan.), 1953.

Rheumatic children receiving corticotropin (ACTH) or Cortisone were given 80 Gm. of carboxylic resin of the hydrogen and potassium types for periods of 43 to 63 days in an effort to minimize sodium retention associated with the administration of these hormones. The potassium content of the resin was suggested as a means of preventing hypokalemia. Analysis of the serum revealed that hypochloremia and alkalosis occurred in spite of the resin therapy. Edema formation was not prevented in patients receiving an unrestricted diet. The additional supply of potassium in the ingested resin did not prevent the development of hypokalemia in four of the five patients treated. It was concluded that these resins were not capable of preventing the acid-base and mineral disturbances induced by corticotropin and Cortisone therapy.

SHUMAN

Samuelson, S.: The Danger of Using Morphine in Cor Pulmonale. Cardiologia **21:** 817 (Fasc. 6), 1952.

The author reviews the literature dealing with the hazard of administering morphine to cases with chronic cor pulmonale and reports 14 cases of his own experience. All except two died. One of the latter was seen twice shortly after receiving morphine and, on both occasions, was on the verge of suffocation. Of the patients with fatal outcome, six were hospitalized in a status asthmaticus. Three of them died three to five hours following an injection of morphine and showed at autopsy a typical cor pulmonale. The other three without the anatomic evidence of cor pulmonale died within 10 to 12 hours following the injection. The rest of the cases who with one exception revealed findings typical for cor pulmonale at autopsy also died within a few hours following administration of morphine.

The author discusses some possible mechanisms involved in the lethal action of morphine in this type of patient and stresses the importance of early intravenous administration of nikethamide and of oxygen therapy as life-saving procedures.

PICK

Spies, T. D., and Stone, R. E.: Effect of Serotonin on Blood Pressure and Lack of Effect of Antimetabolite. J.A.M.A. **150:** 1599 (Dec. 20), 1953.

Persons with hypertension, persons with hypotension, and persons with normal blood pressures were tested by intravenous injections of synthetic serotonin (5-hydroxytryptamine) and with intravenous injections of its potential antimetabolite, 2-methyl-3-ethyl-5-aminoindole. It was found that intravenous injection of serotonin in amounts of 0.5 mg. or more in all persons was followed by a prompt and definite increase in systolic and diastolic blood pressure. Injections of the antimetabolite

seem to be tolerated rather well in all persons tested. Following such injections the blood pressure readings did not go below the base line readings, but the patients with hypertension stated that they felt much more relaxed, and in the only patient with headache due to hypertensive encephalopathy the symptoms disappeared. Repetition of serotonin after the patients had received antimetabolite showed no blocking effect on the action of serotonin. In another study on the effect of oral administration of the potential antimetabolites of serotonin, one patient with hypertension was given 22 Gm. of synthetic 2-methyl-3-ethyl-5-nitroindole orally over a period of eight days. During this period no change in blood pressure occurred. When the last dose of this compound was given, the administration of 0.5 mg. of serotonin intravenously was followed by a rise in blood pressure, indicating that the potential antimetabolite did not block the effect of serotonin.

KITCHELL

Reich, N. E., Rosenberg, B. A., and Metz, M.: The Use of 2-Ethylhexanol in Acute Pulmonary Edema. Dis. Chest **23:** 43, 1953.

Clinical therapy of acute pulmonary edema was tried in 14 unselected cases by means of inhalation of an antifoaming agent. Instead of ethyl alcohol, which had been successfully tried by others, the authors employed octyl alcohol, which has a more powerful antifoaming action in vitro.

Fifty per cent of the patients presented a good response to the inhalation before routine measures were instituted. In some cases relief was dramatic. No toxic reactions were observed and no contraindications are listed. Among the patients submitting to inhalation therapy, six were hypertensive, four had arteriosclerotic heart disease, one had both hypertension and coronary heart disease, two had rheumatic valvular lesions, and one had meningitis.

LUISADA

Harris, A. S., Estandia, A., Smith, H. T., Olsen, R. W., Ford, T. J., Jr., and Tillotson, R. F.: Magnesium Sulfate and Chloride in Suppression of Ectopic Ventricular Tachycardia Accompanying Acute Myocardial Infarction. Am. J. Physiol. **172:** 251 (Jan.), 1953.

Magnesium sulfate controlled the arrhythmia of acute infarction in 46 per cent of cases and the chloride in 70 per cent. Statistically the difference in effectiveness of these two salts is small. One milligram per kilogram injection of either salt reduced mean arterial blood pressure 5 to 30 mm. Hg.

OPPENHEIMER

Yount, E. H., Rosenblum, M., and McMillan, R. L: Quinidine for Chronic Auricular Fibrillation in the Patient Over 60. Geriatrics **8:** 19, (Jan.), 1953.

Normal sinus rhythm was re-established in 119 of 155 patients with chronic auricular fibrillation, or 76.8 per cent. Forty-nine of the 155 patients were 60 years of age or older, and in 41 (84 per cent) of these, the chronic auricular fibrillation reverted to a normal sinus rhythm. In these patients the average plasma level of quinidine at the time of reversion was 8.8 mg. per liter, as compared with a level of 10.2 mg. per liter in patients under 60. It should be noted, however, that in the majority of the younger group the etiologic basis for fibrillation was rheumatic heart disease, although one-third has arteriosclerotic heart disease without any evidence of rheumatic involvement. If only the patients with arteriosclerotic heart disease are compared, the mean plasma concentration of quinidine is identical for both age groups, 8.8 mg. per liter. In the older age group sinus rhythm was restored after shorter periods of treatment and with smaller doses of the drug. Further analysis of the patients over 60 indicates that with advancing age the response to treatment becomes increasingly sensitive.

BERNSTEIN

Kandalla, F. A.: The Use of Oleandrine in Acute Cardiac Conditions. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19:** 399, 1952.

Nerium oleander is a plant whose therapeutic properties were known at the time of Hippocrates. It contains glycosides of the digitalis group. Oleandrine aglycone is composed of gitoxigenin and digitalose, and differs from digitalin only by the absence of one molecule of glucose. It acts like digitalis and strophanthus glycosides but seems more efficient, faster, and noncumulative. Its action on the heart and its diuretic effect are apparent when taken orally. Acute cardiac conditions, left ventricular failure, pulmonary edema, and heart failure with arrhythmias seem the best indications for the use of oleander glycosides.

The author recommends 0.8 to 1.2 mg. daily, divided into three to four doses, for 5 to 15 days. The daily maintenance dose is from 0.4 to 0.6 mg. divided into two to three doses. One tablet contains 0.1 mg. and is equivalent to five drops of the solution.

LUISADA

Friedman, S. M., Friedman, C. L., and Nakashima, M.: The Hypertensive Effect of Compound F Acetate (17-OH-corticosterone-21-acetate) in the Rat. Endocrinology **51:** 401 (Nov.), 1952.

The administration of compound F (17-OH-corticosterone-21-acetate) to young male rats caused a marked suppression of growth, an elevation of blood pressure, an increase in cardiac and renal mass, and a reduction in adrenal size. When minimal doses of compound F were compared with equivalent doses of desoxycorticosterone acetate (DCA), the hypertensive effects of compound F were more pronounced, although heart and kidney weights in the desoxicorticosterone acetate–treated animals were

slightly greater. There were no significant changes in serum sodium and potassium levels in any of the animals studied. The relationship of the etiology of compound F to hypertension warrants further study.

CORTELL

Tanabe, T., Suzuki, T.: A Study of Certain Factors which Influence the Value of Digitalis as Estimated by the Cat Method of Assay of Hatcher and Magnus. Jap. J. Pharm. **2:** 23 (Sept.), 1952.

These experiments were carried out, in order to study the factors which influence the digitalis values obtained by means of biologic assay by the cat method. Sex does not have a significant effect upon the average lethal dose. Cats weighing less than 1.7 Kg. are unsatisfactory, they tend to give results that are variable and often too high. With cats weighing over 1.7 Kg., there was noted a close correlation between lethal dose and body weight. A variation of as much as 10 per cent in values obtained may be expected depending upon the choice of body weight, even if over 1.7 Kg. Fasting for a period as long as four days is permissible provided the cats are sufficiently nourished prior to the onset of fasting. "Muscle-bone index" is considered as an objective index of state of nutrition. Lethal doses remained fairly constant when this index fell within the range 1.8 to 2.4. Below 1.8, variable results were obtained.

BERNSTEIN

Brandfonbrenner, M., and Geller, H. M.: Effect of Dibenamine on Renal Blood Flow in Hemorrhagic Shock. Am. J. Physiol. **171:** 482 (Nov.), 1952.

In standard hemorrhagic shock, at the 50 mm. Hg level, Dibenamine increased renal blood flow when compared with control dogs. After reinfusion the Dibenamine-treated dogs had a somewhat better blood flow. Dibenamine-treated animals had a reduced renal vascular resistance during hemorrhagic shock. Dibenamine did not prolong survival. There was no correlation between renal blood flow and survival in hemorrhagic shock.

OPPENHEIMER

Kandalla, F. A.: Intravenous Treatment of the Acute Pulmonary Edema. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19:** 399, 1952.

The author treated acute pulmonary edema with a slow intravenous injection of a mixture containing 0.5 mg. ouabain, 0.08 Gm. theophylline, 0.10 Gm. procaine, and 20 cc. 50 per cent glucose. This treatment is supposed to terminate attacks of acute pulmonary edema which do not respond to any of these drugs alone or to other drugs. Procaine can be replaced by a triple dose of procaine amide. Theophylline can be replaced by 0.24 Gm. of aminophylline. Ouabain should be omitted in digitilized patients except if there is severe shock or left heart failure. However, the dose of ouabain should be reduced in such cases.

The author mentions procedures which can be associated, such as alcohol vapor inhalations, morphine, barbiturates, oxygen, mercurial diuretics, tourniquets.

Procaine is a sympatholytic drug which balances the effects of sympathomimetic substances, which are liberated following autonomic or diencephalic disturbances.

The author mentions no unpleasant side effects and the results of this combined therapy seemed promising.

LUISADA

PHYSICAL SIGNS

Palfrey, F. W.: Auscultation of the Corrigan or Water-Hammer Pulse. New England J. Med. **247:** 771 (Nov. 13), 1952.

The author emphasizes that the true Corrigan or "water-hammer" pulse is characterized not only by its large volume but also by the transmission of a sudden shock to the examiner's finger over the radial artery. This water-hammer shock is said to represent a pistol-shot sound which can be heard if the stethoscope is placed over the radial artery. If this shock and sound are absent with the arm at body-level, they can be made to appear in some cases by raising the wrist vertically above the head. Such elevation is said to reduce the diastolic pressure at the wrist to a degree measurable, in terms of a vertical column of blood, by the height of the wrist above the heart. Since the diastolic pressure is normally greater than the reduction, no tone appears in the normal person. In certain cases of aortic insufficiency, this elevation is sufficient to lower the diastolic pressure at the wrist to produce the tone. It is recommended that this examination be made in all patients with aortic insufficiency. If no tone is heard over the front of the wrist it may be concluded that insufficiency is slight. If the tone is heard over the wrist but not lower on the arm, the diastolic pressure will usually be 45 mm. Hg. If the tone is heard as low as the elbow, the diastolic pressure will be about 30 mm. Hg.

ROSENBAUM

Stein, E., Schoehnerich, P., and Engelbertz, P.: Phonocardiographic and Cardiodynamic Investigations in Irregular Heart Action. Ztschr. Kreislaufforsch. **41:** 908 (Dec.), 1952.

The authors recorded in cases with auricular fibrillation phonocardiograms together with the carotid pressure curve and the electrocardiogram in order to study alterations of the cardiodynamics effected by the varying diastolic intervals. In the presence of a split second sound, the distance between its two portions was in direct proportion

to the duration of the preceding cycle. This is ascribed by the authors to variations of the filling pressure of the left atrium—high following a short ventricular diastole and low following a long one—which in turn has some effect on the period of rapid ventricular inflow. The time of "ventricular transformation"—defined as the first part of isometric contraction and measured by the distance between Q wave of the electrocardiogram and onset of pressure rise in the arterial curve—varied inversely with the duration of diastole. This phenomenon is explained by alterations of *ventricular* filling relative to the duration of diastole. In addition, it was found that not only the duration of diastole but also the vigor of systole has certain effects upon the duration of isometric contraction, and its subdivisions, of the subsequent heart beat.

PICK

PHYSIOLOGY

Armstrong, W. D., Johnson, J. A., Singer, L., Lienke, R. I., and Premer, M. L.: Rates of Transcapillary Movement of Calcium and Sodium and of Calcium Exchange by the Skeleton. Am. J. Physiol. **171:** 641 (Dec.), 1952.

The authors have calculated that the fractions of plasma calcium transfered to interstitial fluid per minute is 52 per cent. They also conclude that the rates of fractional movement across the capillary membrane of simultaneously injected calcium and sodium are equal. These experiments present evidence that calcium binding by plasma proteins does not interfere with the transcapillary movement of calcium. The change in distribution for calcium between the ionized form and the plasma protein–bound fraction is a rapid one. The authors have estimated the quantities of skeletal calcium and tissue sodium exchanged under conditions of these experiments. There are approximately 44 mEq. of exchangeable sodium per kilogram for the period of 150 to 340 minutes.

OPPENHEIMER

Smith, D. J.: Constriction of Isolated Arteries and Their Vasa Vasorum Produced by Low Temperatures. Am. J. Physiol. **171:** 528 (Dec.), 1952.

When carotid arteries of swine are cooled at a rate of 4 to 6 C. per minute a vasoconstriction results. Flow through vasa vasorum, as measured by transvascular leakage across the vessel wall during perfusion, is decreased by low temperatures. Viscosity of perfusate and constriction in vasa vasorum both play a role. Reaction times to epinephrine, acetylcholine and histamine are increased four- to six-fold at 17 C. One human bronchial artery showed similar reactions to cold.

OPPENHEIMER

Ullrick, W. C., and Whitehorn, W. V.: Influence of Thyroid Hormone on Respiration of Cardiac Tissue. Am. J. Physiol. **171:** 407 (Nov.), 1952.

Respiration of atria in rats made hyperthyroid with desiccated thyroid powder was increased 77 per cent as compared with 22 per cent for ventricles and 33 per cent for diaphragm. Skeletal muscle and smooth muscle respiratory rates were unchanged by similar experiments. Control normal atria and ventricles had ratios similar to one another. The atria and ventricles were not contracting in the Warburg flasks and may be considered basal. The unusual response of atrial muscle to thyroid may be a basis for understanding the arrhythmias and tachycardias of hyperthyroid cardiac disease if it is assumed that oxygen use is related to level of excitation and rate of conduction.

OPPENHEIMER

Robb, J. S.: Specialized (Conducting) Tissue in the Turtle Heart. Am. J. Physiol. **172:** 7 (Jan.), 1953.

In addition to ordinary atrial, ordinary ventricular and smooth muscle, turtle heart contains a tissue which resembles the Purkinje fibers. This specialized tissue extends in scattered bands from the sinus throughout the atria. It forms a good portion of the A-V funnel. The same tissue is distributed deeply and just under the endocardium in the ventricle. Turtle cardiac muscle is not a syncitium. It exhibits unit structure as does mammalian heart muscle. Involuntary muscle in the turtle heart is usually associated with collagen in the sinus and in the atria where it is abundant. In the ventricle smooth muscle is not found with much frequency.

OPPENHEIMER

Lewis, A. E.: Estimation of Plasma Volume of the Heart. Am. J. Physiol. **172:** 203 (Jan.), 1953.

If it is assumed that the right ventricle, pulmonary vascular bed and left ventricle are three simple diluting pools in series, then a mathematical expression may be derived for the dye dilution curve obtained during the measurement of cardiac output. With this equation the volume of each pool may be calculated. Theoretic curves closely approximate experimental ones. The sum of the three volumes thus obtained is approximately equal to the separately determined total volume of thoracic viscera.

OPPENHEIMER

Johnson, J. A., Covert, H. M., and Lifson, N.: Kinetics Concerned with Distribution of Isotopic Water in Isolated Perfused Dog Heart and Skeletal Muscle. Am. J. Physiol. **171:** 687 (Dec.), 1952.

In these experiments the distribution of heavy water was examined in the isolated perfused dog heart and skeletal muscle. The authors are of the opinion, based on the results in this work, that the

results are best explained by the hypothesis that blood flow is the major factor in determining the rate of delivery of heavy water to tissue water.

OPPENHEIMER

Stroud, R. C., and Rahn, H.: Effect of O_2 and CO_2 Tensions Upon the Resistance of Pulmonary Blood Vessels. Am. J. Physiol. **172:** 211 (Jan.), 1953.

Resistance through the pulmonary circuit increased 25 per cent and 48 per cent as oxygen in inspired air decreased to 15 per cent and 8 per cent respectively. Changing carbon dioxide tension of inspired air did not increase the pulmonary resistance. There is evidence that this increase in resistance is associated with vasoconstriction. Thoracic sympathectomy prevented the increase in resistance when 8 per cent oxygen was breathed.

OPPENHEIMER

Wiedeman, M. P., and Nicoll, P. A.: Variations in Response of Minute Vessels in Cecal Mesentery of Rat to Topically Applied Epinephrine. Am. J. Physiol. **172:** 187 (Jan.), 1953.

Stable thresholds were present in less than half the cases when epinephrine was applied locally to the cecal mesentery of the rat using standard procedures. Anesthetic levels influenced the test in a marked fashion. These changes in threshold due to anesthesia were of the same order of magnitude as changes claimed to be significant by other workers. The amount of reaction of vessels and time of onset were variable to standard doses of epinephrine. The authors conclude that shifts in the apparent threshold are inherent in the test. As a result it cannot be used to demonstrate the presence of vasoreactor substances. They also suggest that when animals show a stable threshold, statistically significant shifts in threshold range represent a true threshold change at the effector site but with little evidence as to the nature of the change.

OPPENHEIMER

Lewis, A. E.: Measurement of Thoracic Visceral Plasma Volume. Am. J. Physiol. **172:** 195 (Jan.), 1953.

Plasma volume of thoracic viscera was found to be 42.2 per cent of total plasma volume using the Evans Blue dye curve. The author points out that this figure is about 10 times greater than the figure obtained by direct extraction in anesthetized rats with collapsed lungs.

OPPENHEIMER

Van Harreveld, A., and Lindsley, D. L.: Afferent Innervation of Blood Vessels in the Body Wall. Am. J. Physiol. **171:** 447 (Nov.), 1952.

Vascular pain fibers of the anterior thoracic wall were stimulated by injection of concentrated sodium iodide solution into a mammary artery. The reactions to such painful stimuli are an elevation in blood pressure and a contraction of trunk musculature on the same side. Suitable ligations and low injection pressures restricted the small amounts of solution used to the site of introduction into the artery. This response was not abolished by removal of the sympathetic chain.

OPPENHEIMER

Wright, H. P., Osborn, S. B., and Hayden, M.: Venous Velocity in Bedridden Medical Patients. Lancet **263:** 699 (Oct. 11), 1952.

Using radioactive sodium chloride as tracer, the authors measured venous velocity in the legs of bedridden medical patients. It was found that in hemiplegic extremities a marked reduction in velocity occurred, while in the normal limbs of cardiac patients without complications, no effect was noted during a prolonged period of rest.

It was concluded that only in the completely immobilized extremity is a significant reduction in venous velocity in the legs observed. This is probably related to the failure of the massaging action of the muscles on the blood vessels and to the lack of muscle tone.

ABRAMSON

Robb, J. S.: Concerning Contraction of Heart Muscle. Am. J. Physiol. **171:** 365 (Nov.), 1952.

Evidence is presented that summation and incomplete tetanus do take place in the hearts of small mammals. These data were obtained using a transducer and amplifier along with simultaneous electrocardiograms. Tests were made at various temperatures. In all cases the hearts were perfused and the ventricles were empty. Summation was found when the heart was not hypodynamic. An increase in tension is developed by the summed beat which is greater than that of the normal beat. In the absence of fatigue, tetanus produces an increased tension. It has been reported that heart has unit structure. The author suggests that summation and tetanus take place when additional units are recruited while previously activated units are still contracted.

OPPENHEIMER

RHEUMATIC FEVER

Barrios, H.: Rheumatic Fever and Renal Involvement. Bull. St. Fran. Sana. **10:** 46 (Jan.), 1953.

At St. Francis Sanatorium three types of renal involvement during acute rheumatic carditis have been found. The first type has been called renal epistaxis. This is seen in less than 1 per cent of cases and is associated with nasal epistaxis. It is of sudden onset and is usually severe, demanding transfusions for therapy. Recovery is rapid without evidence of renal damage. Subacute nephritis is seen in a larger number of cases. Of these, 1 in 20 develop into chronic nephritis with classic symptomatology.

With visceral rheumatism a few patients develop chronic glomerular nephritis during the acute rheumatic phase. The renal findings persist when all other visceral manifestations subside. These patients usually succumb to an acute exacerbation of the renal disease.

BERNSTEIN

Wolfe, G.: The Decline and Variation in the Mortality from Rheumatic Heart Disease in the United States. Bull. St. Fran. Sana. **10:** 1 (Jan.), 1953.

The trend in mortality due to acute rheumatic fever and diseases of the heart in the United States is shown for the three year periods, 1919–21, 1929–31 and 1939–41, complemented by data for the single years from 1942 to 1948. The most impressive result is the distinct decrease in mortality among white children, which is in the neighborhood of 80 per cent for the age groups 5 to 9 and 10 to 14 years, and 70 per cent for the older children, 15 to 19 years.

The nonwhite children show no consistent downward trend. In this group, the apparently increased mortality rates, or smaller gains in reduced mortality is probably due to deficient reporting in the early decades of the century. The tendency to higher mortality of the nonwhite group from rheumatic fever and heart diseases in the period, 1939–41, continues in all following years from 1942 to 1948 with not a single exception. From the statistical findings the conclusion is reached that a more unfavorable environment, such as doubtless exists for the nonwhite children, tends to increase the risk of dying from rheumatic fever and its consequences. From age group to age group there is a consistent rise in the mortality rate. This is true for both racial groups and both sexes. The behavior of the sexes shows little significant difference in the mortality rates except in the age group of the older children, 15 to 19 years. In this age group the nonwhite females show distinctly higher death rates than the nonwhite males, while in the white group the reverse is true.

The absolute death toll from rheumatic fever disease in the United States among all persons under 20 years for the three year period, 1939–41, amounted to a minimum of 12,000 deaths, or about 4,000 annual deaths. In the following years the annual death toll has steadily decreased. The highest number of deaths from acute rheumatic fever were reported in the age groups 10 to 14 and 5 to 9 years, in that order, while the chronic aftereffects appear most frequently as cause of death among the 15 to 19 year old adolescents. Mortality from rheumatic fever and diseases of the heart varies considerably among the geographic divisions of the United States. The death rates are below the national average in the three Southern divisions while in the Northeast, especially in the Middle Atlantic division, they are significantly above average. In the Pacific division the death rates are as low as in the South and significantly below the country's average, while in the Mountain division they are exceptionally high for the white children.

The results for the individual states confirm, with a few exceptions, those obtained for the geographic divisions. The progression of low rates in the Southern and Pacific states to significantly high rates in the Northern and especially the Middle Atlantic states points, in addition to the specific-infective agent and social-environmental factors, to the role of certain climatic-geographic influences of the natural environment in the final outcome of rheumatic fever.

BERNSTEIN

BOOK REVIEWS

Electrocardiography in Practice, ed. 3. *Ashton Graybiel, M.D., Paul D. White, M.D., Louise Wheeler, A. M., and Conger Williams, M.D.*, Philadelphia, Saunders, 1952. 378 pages, 294 figures. $10.00.

The third edition of this book maintains its primary aim as an atlas of electrocardiography written for the practitioner of medicine. It is well organized and is divided into eight main parts. The first contains an excellent chapter on the historical development of the physical and physiologic principles upon which electrocardiography is based. The second part deals with methodology. The third part considers the typical normal electrocardiogram and its variations. Chapters are devoted to the electrical orientation of the heart and the relationship of bipolar, unipolar and precordial leads. The use of mean vectors including Grant's method of determining spatial vectors is discussed. It would have been helpful to have had further cases illustrating the value of the QRS-T angle and its application in normal as well as marginal tracings. The fourth part presents in excellent manner the disorders of rhythm and conduction. The fifth part deals with electrocardiographic alterations due to drugs and chemicals. One error is apparent in the statement that epinephrine may "cause upright T waves to become inverted especially in lead II." Any change in the mean T vector will, of course, be reflected in all leads, and if it is negative in lead II it will of necessity be negative in either leads I or III or both by Einthoven's equation. In describing the effects of digitalis no mention is made of the shortening of the Q-T interval.

The sixth part encompasses atrial and ventricular hypertrophy, myocarditis, acute and chronic pericarditis. The simulation of acute pericarditis by T vectors of large magnitude might be pointed out. Such a tracing is shown on page 64. It would have been helpful to include some of the criteria used in determining ventricular hypertrophy such as R/S ratios, etc. The seventh part presents the electrocardiographic findings in a wide variety of etiologic types of heart disease such as rheumatic fever, congenital disease, syphilis, coronary disease, etc. The description of the changes due to pulmonary embolism makes no mention of the S-T depression so common in leads I, II and the left precordial leads or to the less common development of transient right bundle branch block. The eighth part includes a useful section devoted to representative electrocardiograms for practice in interpretation together with concise case histories.

The book will be a ready reference to the practicing physician. It is well illustrated and the legends are on the same or facing pages so that understanding is facilitated.

R. B. Logue

Cardiac Therapy. *Harold J. Stewart, M.D.* New York, Paul B. Hoeber, 1952. 622 pages, 68 figures, 11 tables. $10.00.

This book provides the basic outline for management of heart diseases of all types. The importance of and reasons for well established procedures are presented in detail. Proven newer drugs and treatment methods are selectively incorporated in the recommended programs, with discerning care to avoid displacing the old with the new because it is new. A preview of the most recent advances, as yet untested, is also provided.

Conditions common to many forms of heart disease (congestive heart failure, irregularities of the heart) are specifically considered in separate chapters. Likewise the pharmacologic properties and uses of groups of drugs (for instance, digitalis, anticoagulants) are dealt with separately. This results in many deliberate repetitions as separate cardiac disease entities are later considered. The book closes with a useful section on diets in heart disease. The author has contributed extensively to present medical knowledge of digitalis. Detailed discussion of the digitalis drugs carry his authority into the text. Few physicians will fail to profit by careful reading of this material.

In a book of this sort, the author may present both sides of a controversial issue and leave to the reader the selection of the argument with the greater merit. Conversely, the author may make the choice for the reader. Dr. Stewart has chosen the latter course.

Since most of this book is well written, accurate and valuable, it is easier to single out criticisms than excellencies. A few random examples are noted. The danger of intravenous calcium in a digitalized patient is stated in one chapter, but not in the section where its use is mentioned in the tetany which occasionally follows mercurial diuretics. Some would question the statement that digitalis is used in patients with acute infarction in the same way as in other patients with heart failure. One is left with the impression that ouabain should be considered more than very rarely. The author recommends the full dose of Mecholyl as an initial measure, whereas it is a common precautionary practice to try a small dose first. The effectiveness of streptomycin in the treatment of tuberculous pericarditis is inadequately expressed. The summaries sometimes include new material, valuable in the content of the

ext, but they are of doubtful value to those who vill wish to formulate a treatment program.

This book is recommended for the inexperienced hysician who wishes to survey the treatment pos- ibilities before outlining a course of procedure. The xperienced physician will find it of value in re- iewing a cardiac problem to be sure he has not verlooked some important form of therapy. All racticing physicians will find it useful as a reference o check indications, dosages, and dietary programs n all forms of heart disease.

CALVIN F. KAY

Angiocardiographie et Cathétérisme Cardiaque. Étude critique de leur apport au diagnostic des cardiopathies congénitales. *Pol Cahen.* Paris, G. Doin et Cie, 1952. 188 pages, 41 figures, 5 tables.

The aim of this short review, namely to present critically the value of the contributions made by angiocardiography and cardiac catheterization to the precise diagnosis of congenital cardiovascular anomalies, can be immediately said to have been attained. The author reviews the recent literature on this subject, and it should be noted that the generous bibliography is well chosen, international and entirely up-to-date. To this background he adds his personal experience acquired during his tenure at the Institute of Cardiology in Mexico.

After presenting some generalized statements about each technic in the first two chapters, he devotes the rest of the monograph to comments as to the relative value of the two methods in each of the common anomalies, starting with the septal defects and including patent ductus, coarctation of the aorta and cyanotic conditions. He also devotes a chapter to pulmonic stenosis, which is, however, the least satisfactory as it appears difficult for the author to accept this as a common lesion. He further states that since there is controversy about the findings by catheterization (and here he outlines the argument of Dexter and Dow that congenital dilatation of the pulmonary artery as described by Cournand and Green must in reality be mild pulmonic stenosis) radiographic analysis of the case is the wiser choice. It is regrettable that in the chapter on interatrial defects he does not mention the common association of an anomalous pulmonary vein with this lesion. Rather, one could infer from the presentation that, although it can mimic an interatrial defect in the gas analysis findings, it occurs as a separate entity only. The presentation of findings in the interventricular defects on the other hand, leaves one with the impression that pulmonary hypertension is a common association, rather than one that occurs only in some high septal defects. The evaluation of the two analytic methods in patent ductus is very well discussed and the subject of this malformation in association with marked pulmonary hypertension, with or without reversal of shunt and cyanosis, is clearly presented. A mature consideration of the value of angiocardiography and catheterization in cyanotic patients brings the monograph to a close. The illustrations are of excellent quality, frequently containing useful explanatory diagrams, and the quality of paper and print is very good.

While this volume presents nothing new, nevertheless it is a well-conceived and well-organized review of the usefulness of these procedures in congenital cardiac conditions. It also represents an interesting blending of European and American concepts in this important category of disease.

M. IRENÉ FERRER

Pheochromocytoma and the General Practitioner. *Joseph L. DeCourcy, M.D. and Cornelius B. DeCourcy, M.D.* Copyright by Barclay Newman, 1952. 165 pages.

This small book attempts a comprehensive compilation of available knowledge regarding the various features of pheochromocytoma for the general practitioner. For this purpose, much useful information, extracted from the literature, is presented. Emphasis is given to proper diagnosis, pathology and surgical correction. Unfortunately the book suffers from lack of balance and insufficient condensation of material. Extensive and unnecessary space is devoted to historical background, lengthy case histories and innumerable direct quotations from the literature. The literary style is readable but too often repetitious. The book's value would be greatly enhanced by stating the practical facts about pheochromocytoma for the physician in one-third the original space. A good bibliography of 361 references is appended.

EDWARD S. ORGAIN

La Pression Veineuse Périphérique. *L. Justin-Besancon and P. Maurice. With a foreword by C. Laubry.* Paris, Masson et cie, 1952. 98 pages, 28 figures. 600 francs.

This monograph deals with the physiology and pathology of the venous circulation in general and with conditions maintaining and altering one of the principal factors involved, the peripheral venous pressure. Indirect and direct methods of determination of the venous tension are critically reviewed. The authors prefer direct measurements with a water manometer or an aneroid and consider the normal values to be 8 to 13 cm. H_2O in the supine position.

Abnormalities of the venous circulation are discussed under the headings of venous hypertension and venous hypotension. The authors recognize a syndrome of primary venous hypertension occurring in women with acrocyanosis without other objective evidence of circulatory impairment. Secondary venous hypertension is presented in the order of its principal manifestations: in heart failure, pericarditis, tricuspid lesions and various conditions leading to local elevation of pressure. Venous hypotension is

considered in its relationship to disturbances of the peripheral circulation and to various systemic diseases. A final chapter deals with the response of the venous pressure to therapeutic measures used in the treatment of heart failure and its alterations in the course of improvement of the circulation.

The booklet is easily readable. There is a systematic approach to the problem; the style is clear and concise and the typography is excellent. The main points of the discussion are illustrated by simple diagrams many of which are selected from the literature. A very comprehensive bibliography including pertinent work of Anglo-American authors is given. Thus, this small book completely fulfils its purpose as stated in the introduction, to interest the practitioner in a simple and useful method to aid cardiovascular diagnosis.

ALFRED PICK

Acute Peripheral Arterial Occlusion. *William D. Holden.* American Lectures in Circulation, No. 141. Springfield, Ill., Charles C Thomas, 1952. 66 pages, 2 figures.

This monograph, composed of four chapters, deals with a number of syndromes in the field of peripheral vascular disorders, all of which fall into the category of surgical emergencies. The principal ones discussed are those which cause acute arterial occlusion, namely, trauma to main arterial trunks, arterial embolism, and arterial thrombosis. In each instance the pathogenesis, clinical manifestations, differential diagnosis, and medical and surgical management are presented. Case reports are utilized to characterize or accentuate the clinical story or a mode of therapy. Also included in the text are discussions of traumatic vasospasm and arterial laceration. Very few references to the literature are included; most of the material reflects the author's experience and opinions. For the most part, however, the point of view expressed is the one generally accepted in the field of peripheral vascular disorders.

The volume should prove useful to the surgeon, especially if he is in industrial medicine, to the medical officer in the Armed Forces, and to the cardiologist, faced with the possibility of embolic or thrombotic episodes in his patients. On the other hand, lack of detailed presentation detracts from the value of the monograph to the specialist in peripheral vascular disorders.

D. I. ABRAMSON

Cardiac Pain. *Seymour H. Rinzler, M.D.* Springfield, Ill., Charles C Thomas, 1951. 139 pages, 12 illustrations, 3 tables. $3.75.

This little volume accomplishes what it sets out to do, namely, to acquaint the reader with pain of cardiac origin and its differential diagnosis and treatment. The discussion of these aspects is clearly put down and should be a source of considerable help to medical students and practitioners. The account of the history of angina is sufficiently detailed and interestingly written.

Of importance in this contribution is the author's emphasis on the manner of determining the effectiveness of any medicament in the management of angina. The author and his colleagues have had wide experience in the "double blind technic" of testing pharmacologic agents, and their very profitable experience should be made known to everyone.

There is essentially nothing included about angina as a part of the individual reaction to life situations and experience and, in view of recent work on this subject, this is a serious defect. The author stresses surgical methods of therapy without perhaps enough emphasis on the facts that, with the judicious use of medicaments and the establishment of a good physician-patient relationship, the great majority of individuals with the kind of pain described in this book can be managed effectively.

The author's style is easy to read, the bibliography is extensive and the general arrangement of the book is pleasing.

WILLIAM J. GRACE

Modern Electrocardiography. Volume I. The P-Q-R-S-T complex. *Eugene Lepeschkin.* Baltimore, Williams & Wilkins. 1951. 598 pages, 91 figures, 26 tables. $12.00.

Don Quixote, in looking over the present day deluge of books, booklets, treatises and monographs in the field of electrocardiography would surely once more burst out in anguished lament: "There are those who compose books and toss them out into the world as if they were no more than fritters." Over the years the shift has been to quantity at the expense of thoroughness and the comic strip approach now so popular in presenting problems dealing with the clinical application of electrophysiologic principles has resulted in the erroneous conception that superficial generalizations mean "clarity" and that "shortcuts" (leading to nowhere) can replace the laborious task of acquiring by study accumulated facts and principles.

Dr. Lepeschkin has attempted to block such dangerous trends by an encyclopedic treatment of our knowledge of the form of the electrocardiographic complex. His book is monumental and authoritative and will find its place on any medical book shelf. Dr. Lepeschkin's previous version (of which the present volume is not a translation) was published in German in 1935; the type was destroyed during the war. It still is today the standard reference in European cardiology much as Lewis' "Mechanism and Graphic Registration of the Heart Beat" guided the investigators of an earlier period. In the preface to his own book Lewis remarked that it was written as an abstract of his own observations and that when it was necessary to rely on experiments of others, "I have repeated them wherever it has been possible."

Yet Lewis at that time cited over 1000 references. That Lepeschkin's personal concepts do not dominate the present volume is due to the almost incomprehensible growth of medical writing and to the authors greater respect for and interest in the work of others, which Lewis never had.

Covering a period from 1934 to 1950, the present volume cites almost 10,000 references which have been actively incorporated into the text. Yet very few of the 90 illustrations have been borrowed from others, and in this way, particularly, Lepeschkin has succeeded in setting his personal imprint upon the pages. He has written a book and not simply supervised the collection of biologic data in a handbook fashion. Yet he has managed to retain an objective attitude of submitting facts rather than theories, mindful again of Lewis' statement that "the pure science is to be judged by the paucity of recorded hypothesis."

The scope of the book prevents a detailed discussion of its contents. It begins with three chapters on instrumentation and on the basic laws which govern the distribution of electrical currents in biologic systems. This is followed by a detailed presentation of the normal electrocardiogram and the influences of physiologic factors and physical and chemical agents upon its components, with a chapter on the electrocardiogram of animals. The second portion of the book is devoted to the abnormal electrocardiogram, the data being grouped in the manner that Frank Wilson used in teaching. The serious student will find the presentation of inestimable value in obtaining factual information or in guiding research. The casual peruser will be delighted to find remarks on the electrocardiogram of the grasshopper (§183), and the mole (§197) (which has constant auricular fibrillation), and on the influence of strontium (§540) and the effect of the Laurence-Moon-Biedl Syndrome (§638) on the electrocardiogram.

A special feature of the book is the guiding spirit of Frank Wilson who took a deep and personal interest in its completion. He recognized the volume as one that, in his opinion, obviously was destined to have a lasting influence on clinical and experimental electrocardiography in our time, and he wrote a foreword, a classic piece of medical writing and the last from his masterful pen. He left the scene and the field of science to which he had been so devoted, "in active growth, with fascinating questions still unanswered." Lepeschkin's book has set a milestone. It is a tribute to the past and a challenge to the future.

HANS H. HECHT

Klinische Elektrokardiographie, ed. 5. *Carl Korth.* Urban & Schwarzenberg, Munich. 1952.

Klinische Elektrokardiographie. Lehrbuch fur Studierende und Arzte, ed. 2. *Max Holzmann.* George Thieme, Stuttgart, 1952. 652 pages, 302 figures, 9 tables. DM 69.50.

The two popular German texts on electrocardiography have now appeared in their first postwar revisions. Dr. Korth covers in 300 pages the clinical aspects of electrocardiography in a concise and easily comprehensible description. The discussion of underlying principles is kept to an absolute minimum and clinically significant observations are discussed through the medium of over 180 reproductions of tracings which integrate well with the flow of discussion. The use of precordial leads is relatively supplementary and vectorial analysis is omitted. One wonders whether this approach, which made Pardee's book so popular, is not after all best for the beginner who perhaps needs a background of factual knowledge of patterns before he is confronted with a multitude of perplexing practical and theoretic problems.

Dr. Holzmann's volume is more than twice as long as Korth's book and obviously not designed for a beginner. Its merit lies in the attempted full integration of the various interpretative systems and the continued interfacing of scalar and vectorial presentation of electrocardiographic data. This leads to some curious grouping of the subject matter which seems unnecessarily burdensome. The book comes closer to a discussion of the true nature of the cardiac action current as recorded from the body surface in health and disease than any other clinical text now extant, and it is therefore highly recommended.

Holzmann's book is beautifully printed. Korth's volume suffers from obvious lack of care by the publisher for which there is little excuse.

HANS H. HECHT

Congenital Heart Disease: The Clinico-roentgenologic Picture after the Age of Two Years Based Upon 200 Cases with Cardiac Catheterization. *Henning Gøtzsche.* Copenhagen, Published by the Author, Printed by H. P. Hansens, Bogtrykkeri, 1952. 254 pages, 49 figures, 53 tables. *Danish Kroner 25.*

Dr. Gøtzsche's monograph represents an account of his personal experience with 200 cases of congenital heart disease. Since this is not intended as a textbook of congenital heart disease the usual presentation of etiology and embryology and lengthy discussion of pathologic variation of the various malformations are missing. An introductory chapter informs the reader of the existing technics for the study of congenital cardiac cases and briefly describes methods used by the author's group. Following a chapter surveying the incidence, and the sex and age distribution of the patients in the series, the author proceeds with an analysis of the commoner types of congenital heart disease in the next eight chapters. The clinical features of each syndrome are discussed in detail and findings on physical examination, the results of electrocardiographic and roentgenographic studies are reported and are also presented in table form to show the distribution

and frequency of typical findings and variants. The following two chapters present a summary of findings in a group of cases of rarer syndromes and of cases with uncertain diagnosis. Important points throughout the presentation of the material are illustrated by brief case reports. The final 10-page chapter summarizes the author's analysis of the series as a "clinicodiagnostic survey," which presents the various signs, symptoms, electrocardiographic and roentgenographic findings of the various entities, indicating their incidence in percentages. In an appendix the author tabulates all important findings derived from cardiac catheterization of his patients, including arterial and intracardiac pressures, arterial oxygen saturation, differences in oxygen content of intracardiac blood samples, and the magnitude of shunts expressed in percentage of the total flow.

The book is a well-written report of a sizeable series of well-studied cases of congenital heart disease in which the author compares his own findings with those of other workers in the field. Throughout the discussion the author reveals a sound and critical approach to the subject and helps clarify many issues which are the subjects of controversy. The reviewer found of greatest interest the factual presentation of the material: the tables of frequency of various signs and symptoms and the data contained in the appendix which constitute an excellent reference source for the range of findings in the various entities. The book is highly recommended not only to those engaged in investigative work in the field of congenital heart disease but also to clinicians interested in this subject who will find much valuable information which is helpful in arriving at clinical diagnosis.

ARTHUR SELZER

Deformation and Flow in Biological Systems. *Edited by A. Frey-Wyssling.* Amsterdam, North-Holland Publishing Company, and New York, Interscience Publishers, 1952. 552 pages, 107 figures, 19 tables. $11.50.

This is a significant collection of essays which are devoted to so widely different subjects that not many readers will study the book from cover to cover. Those interested in circulation will be attracted mainly by two chapter which deal with the elastic properties of muscular tissues, and with the rheology of the blood flow, respectively.

The first mentioned topic is the subject of a contribution by M. G. M. Pryor entitled "The Rheology of Muscle." In this discussion, which is of a more general nature (not specifically referring to cardiac or other types of muscle), the author gives a competent discussion of contraction and deformation in terms of the mobility of the chains of a protein (although it is known that two different proteins, myosin and actin, are involved). The importance of such a formalistic, if restricted, approach to muscle elasticity cannot be denied, but it is probably of very limited applicability to the study of the contraction process itself.

Of more direct circulatory interest is a chapter by L. E. Bayliss on "Rheology of Blood and Lymph," comprising nearly 70 pages, in which a well-rounded discussion is given without the use of advanced mathematical tools, and with full attention to experimental details. Some of the latter are taken from the author's unpublished work, and refer, among others, to observation on the flow of blood in glass capillaries as narrow as 7 microns. However, the chapter does not deal with such in vitro work only, but discusses also the flow of blood in the living body. A short chapter by Hermans discusses some aspects of flow through elastic capillaries, but this important contribution is on a very advanced physical level.

Other chapters are devoted to cerebrospinal and intraocular fluids, to secretions, and to a variety of topics of general biologic interest. At the end of the volume, one finds abstracts and discussions of the First International Colloquium on Rheological Problems in Biology, held at Lund in 1950, including communications on blood flow by Farhaeus and by Potter and McDonald.

W. F. H. M. MOMMAERTS

AMERICAN HEART ASSOCIATION, INC.

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APPLICATIONS FOR GRANTS-IN-AID

Applications for research grants-in-aid for the Association's 1954–55 fiscal year must be filed by December 1, 1953. Information and application forms may be obtained from the Medical Director.

SCIENTIFIC PROGRAM OF SECTION ON CLINICAL CARDIOLOGY

The Section on Clinical Cardiology of the American Heart Association will sponsor a two-day scientific program at the Conrad Hilton Hotel in Chicago on April 3 and 4, 1954. This program will follow the Annual Meeting of the Assembly of the American Heart Association and will immediately precede the Annual Sessions of the American College of Physicians. The meeting will be open to all members of the medical profession. Wright R. Adams, M.D., Chicago, is Chairman of the Program Committee. Members of the American Heart Association who wish to present papers should send a 250 to 300 word abstract of the proposed paper to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y. All papers should be on subjects of distinct clinical interest. The deadline for receipt of abstracts is Jan. 1, 1954.

1954 SCIENTIFIC SESSIONS

The Twenty-Seventh Scientific Sessions of the Association will be held in Washington, D. C., during the week of Sept. 12–18, 1954, in connection with the Second International Congress of Cardiology, which will be held in Washington Sept. 12 through 15, 1954. Members of the International Congress are invited to attend the Scientific Sessions. Admission will be by Congress badge.

LIFE INSURANCE FUND RESEARCH FELLOWSHIPS AND GRANTS

The Life Insurance Medical Research Fund has announced the following deadlines for applications for awards available July 1, 1954:

(1) Oct. 31, 1953, for postdoctoral research fellowships. Preference will be given to those who wish to work on cardiovascular function and disease or related fundamental problems. Stipends vary from $3,300 to $4,500.

(2) Nov. 15, 1953, for grants to institutions, in aid of research on cardiovascular problems. Support is available for physiologic, biochemical and other basic work broadly related to cardiovascular problems, as well as for clinical research in this field.

Additional information and application blanks may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46 Street, New York 17, N. Y.

REMINDER NOTICES

Heart Models

The series of twelve life-size rubber reproductions of normal and diseased hearts, developed by the Association for use as visual aids in medical teaching, may now be purchased painted with fluorescent pigment in several colors, as well as unpainted. A descriptive folder and complete price list may be obtained on request to the Association.

Recent Publications

Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels ($4.95, clothbound). The completely revised and greatly expanded Fifth Edition of this standard reference work, published by the New York Heart Association and distributed by the American Heart Association, introduces some entirely new concepts and viewpoints developed in the past ten years. Copies may be obtained from affiliated Heart Associations or medical bookstores.

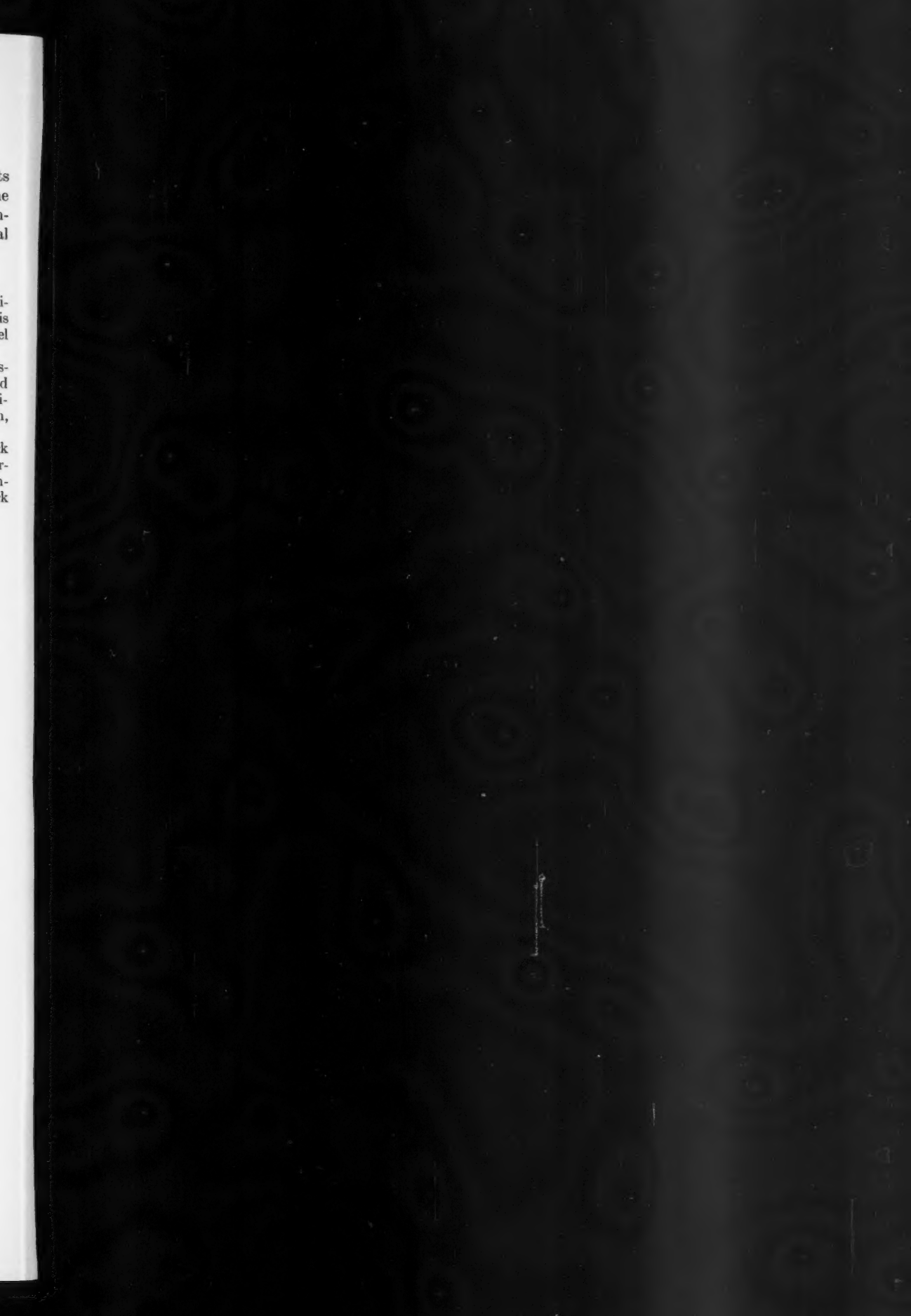
Films in the Cardiovascular Diseases: Survey, Analysis and Conclusions, by David S. Ruhe, M.D., and associates ($1.50 paperbound; $2.00 clothbound). Directed to those interested in or concerned with using films in medical teaching, this volume reviews 62 available films in the cardiovascular field and lists 118 others. It is a joint publication of the Association and the Medical Audio-Visual Institute of the Association of American Medical Colleges.

MEETINGS

Nov. 1–2: American Society for the Study of Arteriosclerosis; Hotel Knickerbocker, Chicago. Louis N. Katz, M.D., Program Chairman, Michael Reese Hospital, Chicago 16.

Nov. 6–7: Fifth Annual Symposium on Heart Disease; Washington State Heart Association and Washington State Department of Health; University of Washington Medical School Auditorium, Seattle.

Nov. 20: "Heart-in-Industry" Conference, New York Heart Association; Hotel Statler, New York. Norman Plummer, M.D., Chairman of Steering Committee, New York Heart Association, 270 Park Avenue, New York 17.



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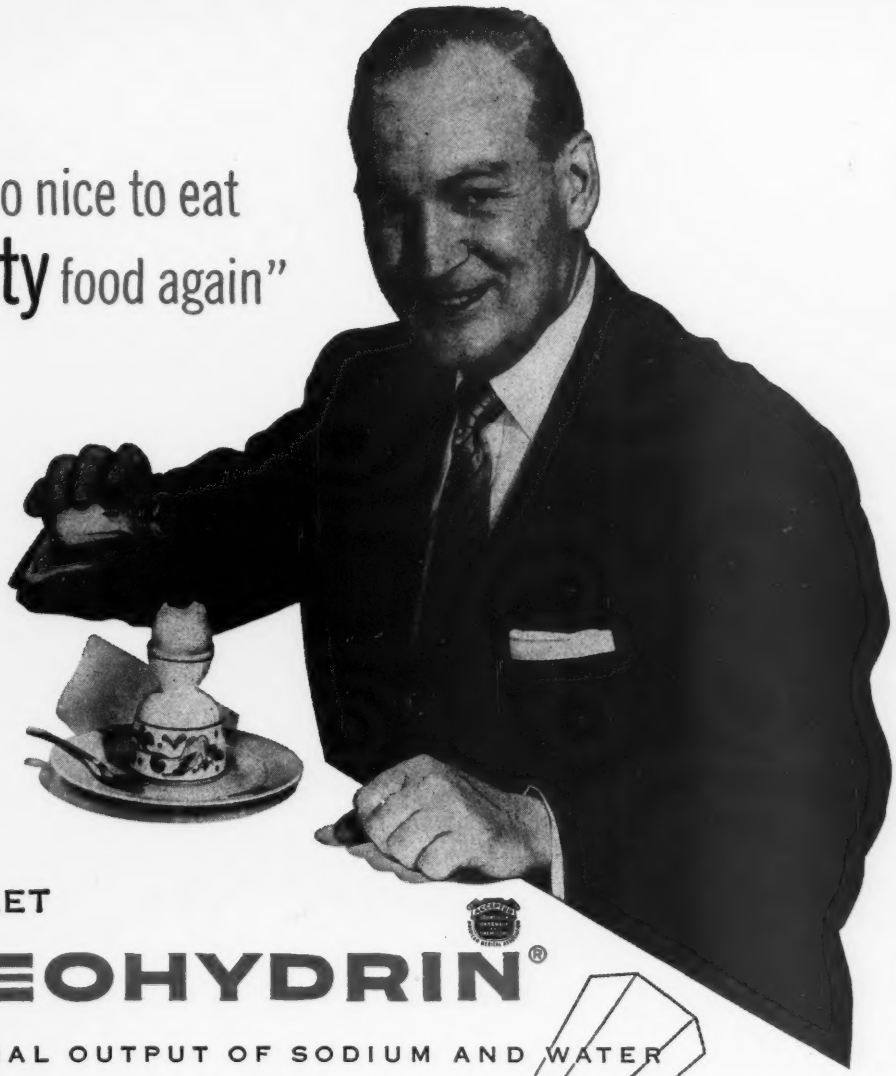
tasty food again"



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